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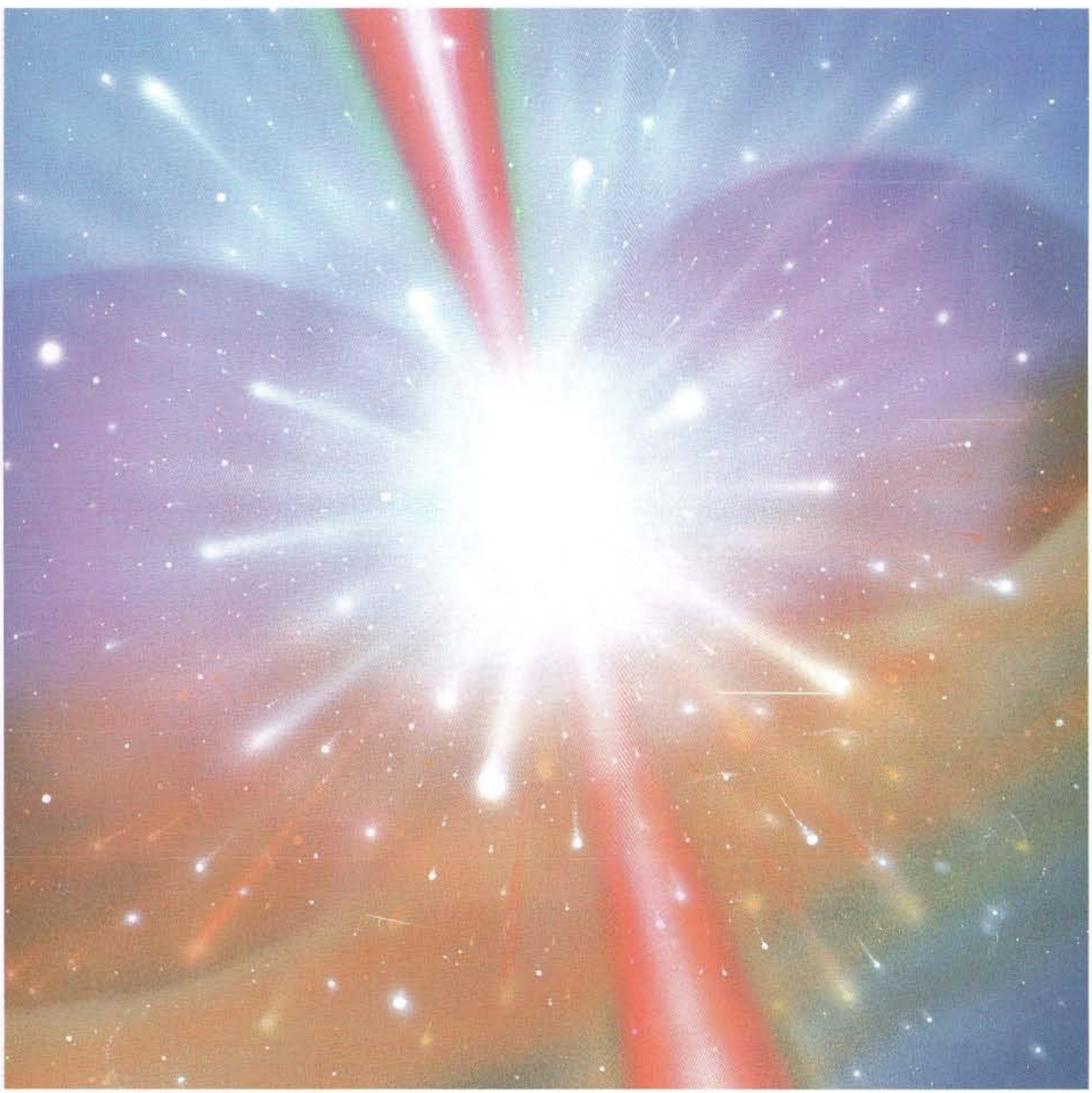

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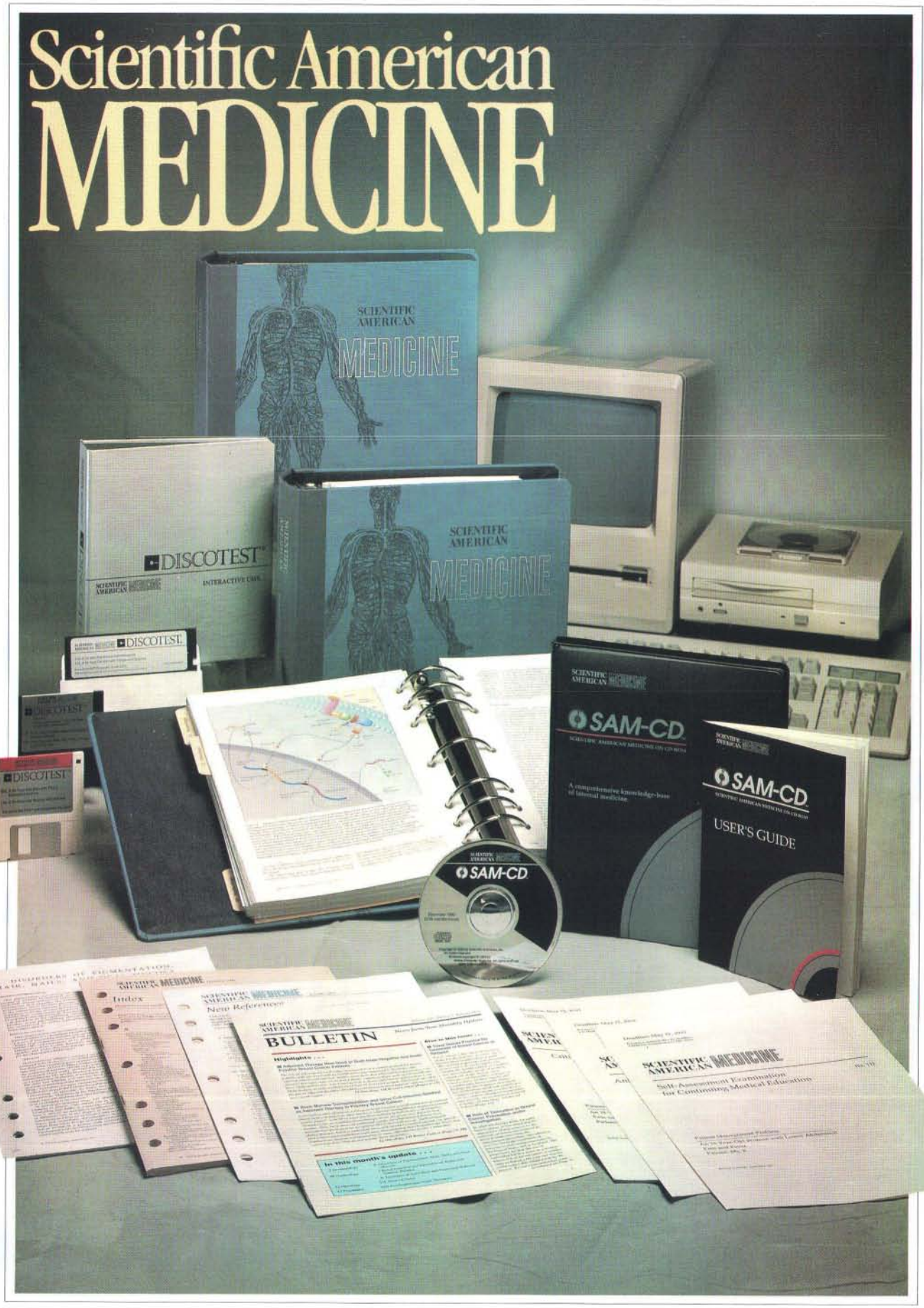

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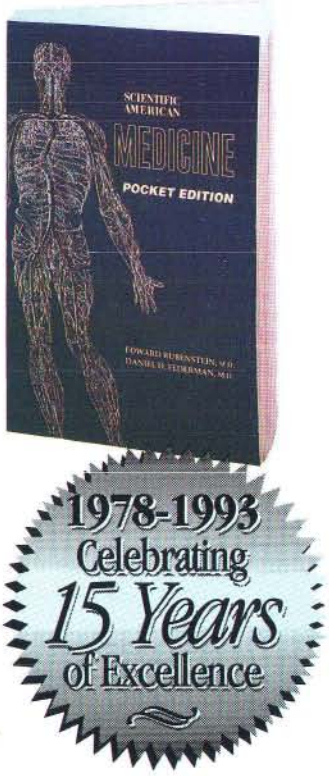

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THE COVER painting depicts one of the most violent and energetic events in the cosmos: the collision of two neutron stars. As the stars meet, their fierce gravity tears them each apart, giving rise to a brilliant blast of radiation and two opposed jets of high-speed particles. Merging neutron stars may be responsible for the peculiar bursts of gamma rays that come from all directions in the sky (see "The Compton Gamma Ray Observatory," by Neil Gehrels, Carl E. Fichtel, Gerald J. Fishman, James D. Kurfess and Volker Schönfelder, page 38).

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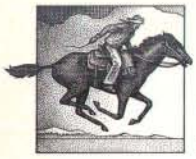


LETTERS TO THE EDITORS

Not So Fast

I enjoyed "Faster than Light?" by Raymond Y. Chiao, Paul G. Kwiat and Aephraim M. Steinberg [SCIENTIFIC AMERICAN, August]. It is one of the clearest expositions of experiments on nonlocality that I have seen. But I must take issue with the statement that one of the most fundamental tenets of modern physics is the proposition that nothing travels faster than the speed of light.

To say that relativity allows *nothing* to travel faster than the speed of light is overstating the case. In an article called "Things That Go Faster than Light" [SCIENTIFIC AMERICAN, July 1960], I called attention to the fact that a number of phenomena do. Notable among these are microwaves in a waveguide and certain electromagnetic waves in a plasma. This fact, for example, is responsible for the reflection of radio waves from the ionosphere. The catch is that these superluminal velocities apply only to the so-called phase velocity of steady waves. If you modulate these waves to transmit information, the signal travels with the group velocity, which is always less than the speed of light.

MILTON A. ROTHMAN
Philadelphia, Pa.

Multiple Sensitivities

In "Allergy and the Immune System" [SCIENTIFIC AMERICAN, September], Lawrence M. Lichtenstein may have inadvertently misled your readers regarding the status of people who are, as he says, "'sensitive' to their environment." It is a mistake to confuse various nonallergic adverse responses with IgE-mediated allergic responses. Therefore, it is also a mistake to conclude (as unwary readers of this article might) that there are no such nonallergic responses and that those who say otherwise are "wasting millions" of "already limited federal research dollars."

Bluntly stated, allergy is not the only well-documented response to various environmental exposures. For instance, there is intolerance for the sugar lactose caused by a deficiency of the enzyme lactase. Respiratory hypersensitivity from contact with isocyanate compounds has been documented. So, too, has reactive airways dysfunction syndrome, in which an initial exposure to a chemical causes a person's airway to react to subsequent exposures. Airway reactivity to sulfur-containing compounds has also been reported. None of these conditions is considered to be of an allergic nature, and all of them have been described in peer-reviewed journals.

In 1991 the National Research Council (NRC), together with the Environmental Protection Agency, sponsored a workshop on multiple chemical sensitivities. The workshop's recommendations reflect widespread agreement about what needs to be learned about adverse health effects from low-level chemical exposures. Research to answer questions noted by NRC workshop participants can hardly be considered a waste of limited federal dollars.

LOUISE KOSTA
The Human Ecologist
Atlanta, Ga.

No Chaos Here

Hogwash! The circuits described in "The Amateur Scientist," by Joseph Neff and Thomas L. Carroll [SCIENTIFIC AMERICAN, August], do not demonstrate synchronization of two chaotic systems. Instead the authors have merely shown that two identical nonlinear filters behave similarly when the same driving function is applied to both.

If you remove the stimulus from the driven circuit and look for its output, the result is...nothing. The two circuits are likely to become unsynchronized because of variations in the devices themselves and, more important, because of the random noise present in each of the circuit elements. The "synchronized circuit" does not behave chaotically and is certainly not an oscillator.

PAUL NEHER
Las Cruces, N.M.

Carroll replies:

Although there is noise in the circuit, the unusual behavior is truly chaotic and can be reproduced in noise-free numerical simulations. That two identical nonlinear filters will behave similarly when the same driving function is applied to both is not always true, and it is not what the column states. The nonlinear filters behave similarly only if they are stable with respect to the driving signal. Neher also states that the response circuit "does not behave chaotically and is certainly not an oscillator." This is true; in fact, this is why chaotic synchronization works.

The most important idea behind chaotic synchronization is that one may take apart a chaotic dynamic system and reconstruct it to fit some particular application. I can send papers on this subject to anyone who is interested.

A Sensation of Nausea

It seems insensitive and unnecessary to include the comparison of collecting cards of endangered species with those of Jeffrey Dahmer and other serial killers ["I'll Trade You a Wallaroo for an Aardvark," by Gary Stix; "Science and Business," SCIENTIFIC AMERICAN, August]. The tradition of trading baseball cards is a time-honored pleasure, literally passed down from generation to generation. Collecting cards of mass murderers has a sick implication. I suspect that interest in these cards is momentary, generated by a large advertising budget and a slow news week. Why mention them? They add nothing to the article but a sensation of nausea.

LIZETTE R. CHEVALIER
Holt, Mich.

Never Look Back

Eight and a half billion dollars for a Super Collider to find out how the universe began is too much money. I say forgive and forget, and let's get on with our lives.

HENRY H. GROSS
Seattle, Wash.

Letters selected for publication may be edited for length and clarity.

ERRATUM

The illustration and caption on page 32 of the September issue require clarification. The cells that interact with class II MHC molecules become helper *T* cells. The cells that interact with class I MHC molecules become killer *T* cells.

50 AND 100 YEARS AGO

DECEMBER 1943

"Penicillin, the magical drug derived from the mold *Penicillium notatum,* may be the greatest single medical discovery of this age, but the case is not yet proved. Indeed, no one can state with assurance which types of infection will and will not yield to treatment. Nor is it entirely certain that penicillin is, as it seems to be, entirely free of dangerous reactions. To settle such matters, sufficient quantities are needed for study. However, the desperate need for production of this drug fails to excite the mold; infinitesimal quantities are all that it will yield. But change is coming. In the characteristic American tradition of co-operation, the problems of penicillin are under attack by the most expert team that can be assembled; formation of the team gives promise that the problems of providing ample quantities will be solved as quickly as possible."

"A new anti-sabotage weapon in the form of an electronically operated X-ray apparatus makes possible the safe, instantaneous, non-destructive, fluoroscopic, and radiographic internal examination of incoming and outgoing packages and small luggage at war plants, air and railway express offices, post offices, police stations, and so on. To operate the unit, manufactured by North American Philips Company, Inc., it is only necessary to plug it into a standard 110 volt AC power source, open the compartment door, insert the object, close the door, push a button, and view the internal structure through an eye-level eyepiece. No skill is required."

"Unless new oil fields are found, the United States may be forced to import oil from abroad and also use more coal of low grade for power generation.—*E.G. Bailey, Vice President of the Babcock and Wilcox Company.*"

"The possibility that American motorists may be zipping over steel highways soon after the war looms as a result of an experimental installation of a steel roadway strip on a Connecticut highway. Sponsors of the highway project—the town of Darien and the Irving Subway Grating Company—feel that if it proves successful, it may well set the pattern for a network of steel secondary roads throughout North and South America. The technique calls for interlocking steel grating panels, each 2 feet by $12\frac{1}{2}$ feet; filling the mesh with ordinary construction sand; and then applying a coating of road oil."

SCIENTIFIC AMERICAN

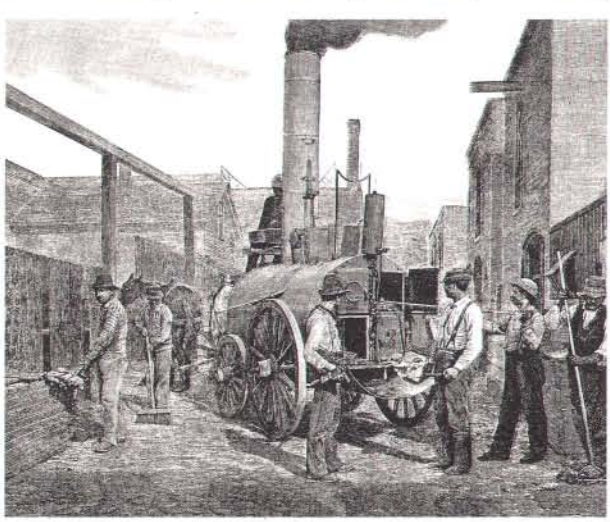
DECEMBER 1893

"What Sir R. Ball has to say concerning the movements of the molecules in a diamond is truly surprising. Every body is composed of extremely, but not infinitely, small molecules. Were the sensibility of our eyes increased so as to make them a few million times more powerful, it would be seen that the diamond atoms are each in a condition of rapid movement of the most complex description. Each molecule would be seen swinging to and fro with the utmost violence among the neighboring molecules and quivering from the shocks it receives from the vehement encounters with other molecules."

"Photography has enabled the astronomers of today to see that which their brethren of a few years ago had never dreamed. In a recent lecture in San Francisco, about sixty stereopticon views were presented. In images of Mars, the trained eye of the astronomer detects little green spots, believed to be water, and others supposed to be land. At the poles are white spots, evidently ice and snow. The great comet of 1882 was reproduced with startling effect. This comet has a tail 100,000,000 miles long, and will not be again visible until 800 years have passed."

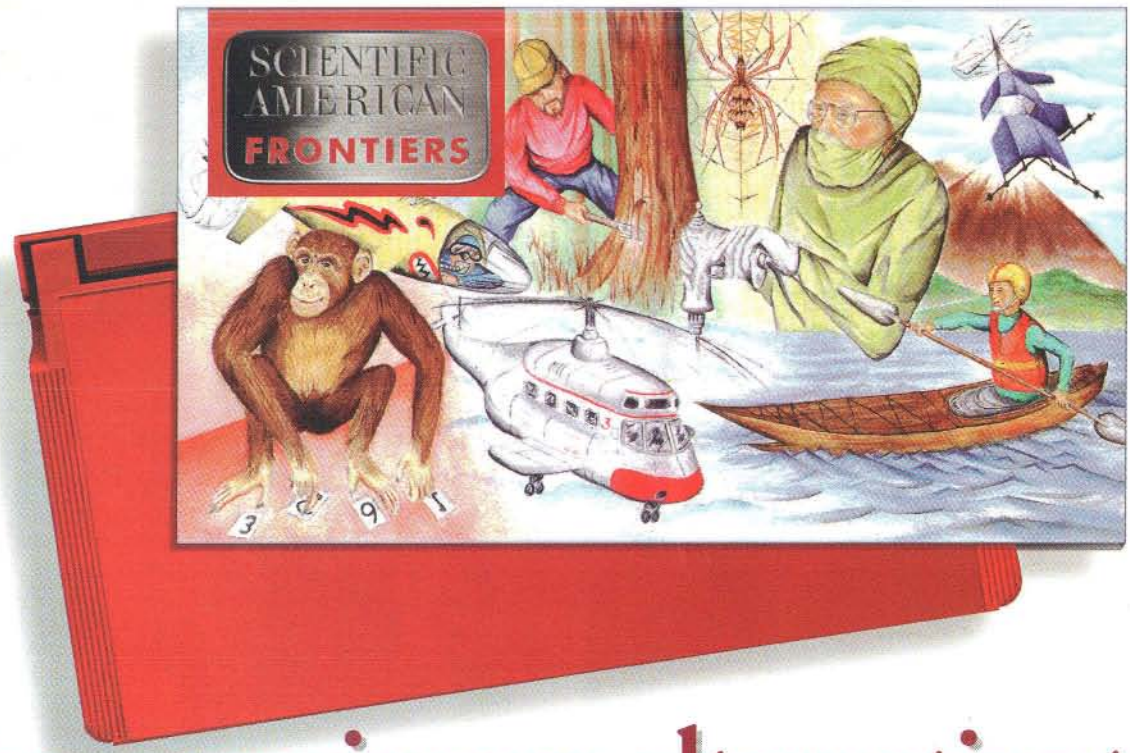
"On the evening of December 4, Prof. John Tyndall died. He was associated with Faraday in his work at the Royal Institution of Great Britain. He was appointed to the chair of Natural Philosophy there in 1853, and after Faraday's death in 1867 succeeded him as superintendent. His wife was the innocent cause of his death. He had been ill for some time, and was taking both chloral and sulphate of magnesia. By mistake his wife gave him a large dose of chloral, thinking it was the magnesia. As she realized what she had done, she told him. He cried, 'You have killed your John.' He jumped out of bed and called for a stomach pump. But his life could not be saved. The fatal dose was taken at 8:30 A.M., and death occurred ten hours later, at 6:30 P.M."

"Municipal governments commonly remove garbage by means of carts that go from house to house gathering whatever refuse there may be. When the carts are loaded, they ride through the streets with the foul-smelling and disease-breeding load to a distant dump. Not satisfied with the carts or with existing stationary and portable crematories, Superintendent Welles, of the street-cleaning department in the city of Chicago, has devised a horse-drawn crematory that has produced decidedly satisfactory results. On the top is a receiving box into which the garbage is thrown. When the box is filled, a rod attached to the sliding bottom is pulled out and the contents dropped into the furnace below. A wagon that follows the crematory gathers up ashes and refuse that cannot be consumed. It is estimated that this outfit of traveling crematory and the two refuse wagons that follow it will take the place of fifteen to twenty ordinary garbage wagons."



Traveling garbage burner of Chicago

Illustration by Carl A. Semmler



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Challenges for 1994

The end of 1993 reminds us that science is the force that prevents history from repeating itself. By creating knowledge with which to control nature or adapt to it, science breaks the pattern, turning what would be a cycle into a spiral—usually, but not always, upward bound.

Science has the power to change both society and itself because answers always breed new questions. The following pages present some of the most exciting discoveries of 1993 and the questions they raise for 1994.

The sun really does appear to produce fewer than the predicted number of neutrinos. Why? The answer may provide a glimpse of a unified theory of nature. An accelerator called a *B* meson factory is being planned that may reveal why there is more matter than antimatter in the universe. The answer could be lighting living rooms in the next century.

Meanwhile work in condensed matter physics may have important consequences tomorrow. Does porous silicon really emit light? The answer seems imminent. Designers of computing and communications hardware hope it is positive. Business communications have taken to the airwaves. How can the information be compressed to avert radio-frequency gridlock? Can artificial materials harder than diamond be coaxed—economically—out of carbon? What uses are there for the prodigious energy released from molecules by collapsing bubbles?

A new mechanism for cancer has been discovered. Will clinicians be able to employ the knowledge in treatment and prevention? Two medical developments, gene therapy and the external liver-assist device, are approaching clinical usefulness. They may extend life, but they also force medicine into uncharted moral territory. Does the human mind have a center that integrates information into perception? The answer is challenging—and disturbing.

Not all questions emerge from the laboratory. Greenland ice cores suggest that climate can change suddenly and radically. Would we have time to adapt if global warming precipitates a shift? But there is always hope. The giant ground sloth may still survive in the Amazon. Perhaps extinction is not always forever.

Enough policy issues have emerged to keep an entire Brookings Institution awake all night for at least a year. Can Billary make the Superfund work? Will a cold war defense R&D policy produce the armamentarium we need for security in the new world disorder, or will it be business as usual at the Pentagon? Can hard-pressed corporations afford to treat research facilities as current liabilities?

The coming months will measure how well we cope with the problems and capitalize on the opportunities that the discoveries and advances of 1993 have created. Only one fact is certain: the world will never be the same again.

—*Jonathan Piel*

Heart of the Matter

A particle "factory" for probing a seminal asymmetry

On this side of the Atlantic at least, these are anxious days for particle physicists. Letters in *Physics Today* and other journals agonize over the future of the field, and circumstances justify the anxiety. A poor economy has kept the Superconducting Super Collider (SSC) teetering on the edge of political death. Many physicists fear that their discipline, lacking experimental results from ever higher energies for guidance, may become lost in a mathematical wasteland.

Yet there are signs of vitality. On October 4 the Department of Energy announced its intention to build a facility at the Stanford Linear Accelerator Center (SLAC) for probing one of the fundamental mysteries of modern physics, a phenomenon called *CP* (for charge parity) violation. The $200-million instrument will not achieve anything like the energies necessary for revealing the SSC's most celebrated quarry, the fabled Higgs boson, which might explain why particles have the seemingly arbitrary masses they do. On the other hand, the planned Stanford facility may answer a question that is not exactly trivial: Why is there something rather than nothing in the universe? "It really is a beautiful set of experiments, and it is a cost-effective way to do them," says Stanley B. Kowalski of the Massachusetts Institute of Technology, who chaired a committee that advised the DOE on its decision.

The roots of the *CP*-violation puzzle reach back to experiments done more than 30 years ago showing that matter and antimatter are linked by deep symmetries. Any process energetic enough to create particles will produce an equal number of antiparticles. When particles and antiparticles collide, they vanish in a burst of pure radiation. Moreover, antiparticles generally behave like oppositely charged, mirror images of their particle counterparts (if a particle spins clockwise, for example, its antiparticle

will spin counterclockwise), obeying what came to be known as charge-parity conservation.

By the early 1960s many physicists had concluded that *CP* conservation was a stricture as absolute as the conservation of energy. They were therefore stunned in 1963, when experiments by Val L. Fitch and James W. Cronin showed that not all interactions follow the charge-parity rule. "It was totally unexpected," recalls Fitch, who is at Princeton University. He and Cronin found that particles called *K* mesons transmute into their antiparticles slightly less often than the antiparticles change into *K* mesons.

Although some theorists viewed *CP* violation as an unsightly deviation from the overall symmetry of physics, the Soviet physicist Andrei Sakharov realized it might solve what was emerging as a central problem in cosmology. The primordial explosion in which the universe was conceived should have spawned matter and antimatter in equal proportions. Over time, each particle should have encountered its antiparticle, and eventually all matter would be replaced with a glimmer of gamma rays. The obvious question is, How is it that so much matter managed to survive and so little antimatter?

In 1968 Sakharov suggested that *CP* violation might hold the key to this puzzle, which is sometimes called matter-antimatter asymmetry. During the big bang, Sakharov speculated, an asymmetry related to the effects observed by Fitch and Cronin could have led to the production of slightly more particles than antiparticles.

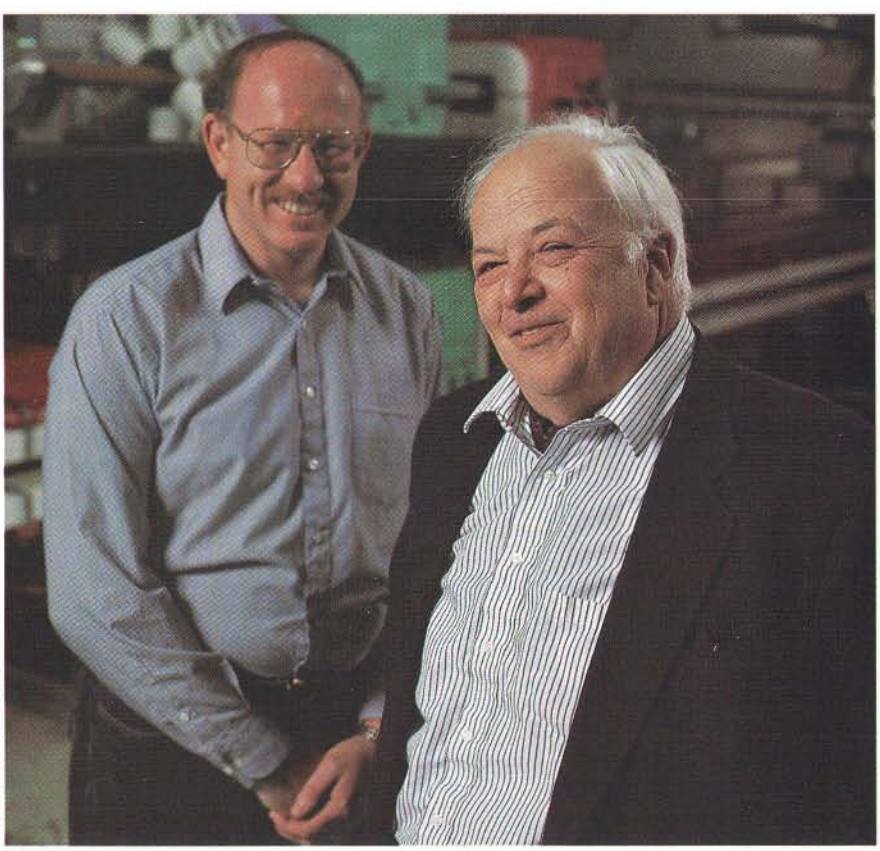
Sakharov's proposal served as the seed for a thriving field of inquiry. In the 1970s, for example, Lincoln Wolfenstein of Carnegie Mellon University suggested that an additional, extremely weak force of nature might cause *CP* violation. In the early 1980s theorists suggested that *CP*-violation effects created matter during inflation, a period of extremely rapid expansion occurring during the first 10^{-35} second after the universe's birth. Several years ago a group led by Michael Dine of the University of California at Santa Cruz and Larry D. McLerran of the University of Minnesota proposed an alternative theory, which holds that matter began to predominate over antimatter during a later epoch, after inflation had ceased.

Unfortunately, experimentalists have been unable to test these theories rigorously. "*K* mesons can't pin down the *CP*-violation mechanism," says Karl Berkelman of Cornell University, which has a small facility for meson research. *K* mesons display *CP* violation so rarely (fewer than one in 500 interactions) that physicists could not study the effect in any detail, no matter how many of the interactions scientists could generate in an accelerator. Moreover, Berkelman explains, *K* mesons have relatively low masses, and their effects are often masked by those of other particles.

Physicists have therefore pinned their hopes for understanding *CP* violation on the *B* meson, which Jonathan M. Dorfan of Stanford calls the *K* meson's "heavy brother." *B* mesons are similar to *K* mesons, except that they are composed of bottom quarks rather than lighter strange quarks. Theorists estimated a decade ago that to study *CP* violation fully will require generating *B* mesons in amounts well beyond the capability of any current accelerator. Thus was the idea for the "*B* factory" born. The Stanford facility will generate *B* mesons by boosting electrons and their antimatter twins, positrons, to high energies in separate rings and then smashing them together.

In addition to solving the *CP*-violation mystery, the *B* factory could lead to a deeper understanding of the forces of nature, according to Dorfan, who led the SLAC team that put together the *B* factory proposal. The Standard Model of particle physics makes predictions about how—and how often—*B* mesons should display *CP* violation, he explains. If experiments diverge in a significant way from those predictions, Dorfan says, theorists may be forced to overhaul the Standard Model or seek a new theory. Dorfan's personal view is that "the present theory is not correct."

Michael Riordan, another SLAC physicist, says he cannot understand why some of his colleagues are afraid their discipline is approaching a cul-de-sac. He notes that researchers are currently engaged in a number of exciting experiments. Some involve attempts to find the top quark, a vital but still unobserved component of the Standard Model. Others are aimed at determining why the sun seems to emit fewer neutrinos than it should [*see page 24*]. "Experimentally," Riordan says, "there are lots of things to do." —*John Horgan*



FRED MERTZ PHOTOGRAPHY

B *FACTORY is scheduled to be built at the Stanford Linear Accelerator Center. Burton Richter, SLAC's director* (right), *and Jonathan M. Dorfan helped to convince the Department of Energy to build the facility at SLAC.*

From Mice to Men

The burgeoning business of gene therapy

Three years ago W. French Anderson, then at the National Institutes of Health, made medical history when he treated a four-year-old girl suffering from a rare genetic disease by adding a functioning gene to the cells of her immune system. The attempt seemed bold and chancy, an isolated harbinger of therapies that just might over time find more widespread use. Few observers expected that by the end of 1993 literally dozens of gene therapy trials would be under way.

Investigators conducting the trials are attempting to treat not only inherited diseases but also infections and several types of cancer. By late this year slightly more than 160 patients around the world had received gene therapy, notes Anderson, who is now at the University of Southern California. "What's happening is that gene therapy, which has until now been carried out in academic institutions, is shifting into commercial enterprises," he says.

Fifteen biotechnology companies have made gene therapy their primary objective, and other firms are active in the area. In its simplest form, the approach consists of transferring a functional gene to a patient's cells to take over from a gene that is defective. In his inaugural effort, Anderson used a disabled retrovirus to transfer a working gene for adenosine deaminase into a patient's blood cells in the laboratory, then reintroduced the blood cells back into the patient. The procedure enabled her and two other patients to develop nearly normal immune systems. This year researchers incorporated a modification they hope will enable the new genes to be taken up by long-lived cells called stem cells. If that works, patients may not even need follow-up treatments. The apparent success of the retrovirus technique means it is now being applied to other conditions.

In a variation on the theme, researchers at the National Cancer Institute and the National Institute of Neurological Disease and Stroke have attempted to treat patients with inoperable brain cancer by sensitizing their tumors to an antiviral drug. Tumor cells are deliberately infected using a retroviral "vector," in the jargon of the trade, containing a gene from a herpesvirus that makes the cells sensitive to the antiherpes drug ganciclovir. Unlike Anderson's original technique, this approach transfers genes to tumor cells in situ—mouse cells that produce the modified retrovirus are injected into the brain, thus avoiding the need to culture human cells outside the body. R. Michael Blaese, chief of cellular immunology at the National Cancer Institute and one of Anderson's original collaborators on the first gene therapy, says five out of the initial eight patients treated have shown "an objective response."

As Anderson observes, gene therapy exemplifies the flowering of the new bioscience-industrial complex. Many protocols use materials developed by Genetic Therapy, Inc., in Gaithersburg, Md., which has a commercial relationship with Anderson. In progress are trials for several types of cancer, including melanoma and leukemia.

Another company that has close ties with top researchers in academia is Somatix Therapy Corporation in Alameda, Calif. One of its founders was Richard C. Mulligan of the Whitehead Institute at the Massachusetts Institute of Technology, who has developed important retroviral vectors. Inder Verma of the Salk Institute for Biological Studies in La Jolla, Calif., also collaborates with Somatix. Some individuals in the field credit Verma with having made the most progress toward finding ways to maintain stable, long-term activity of transplanted genes.

Two years ago Verma transplanted into a mouse a gene for factor IX, a protein essential for blood clotting. The mouse is still producing the protein, a lack of which causes hemophilia B. Somatix is working on therapies for the more common type of the disease, hemophilia A. It is also aiming at a therapy for Parkinson's disease, which is caused by a shortage of dopamine in the brain. That defect might be corrected by adding the gene for tyrosine hydroxylase, an enzyme essential for producing dopamine.

In an experiment just begun at the Johns Hopkins University School of Medicine, researchers will use a Somatix retrovirus to add a gene for a blood cell growth factor known as GMCSF (for granulocyte-macrophage colony-stimulating factor) to cells from tumors removed from kidney cancer patients. When the modified cells, irradiated to stop them from reproducing, are reinfused into the patients, Drew M. Pardoll and his colleagues expect them to unleash a powerful immune system attack on any tumor cells remaining. In tests with mice, the GMCSF gene stimulated long-lasting immune responses to tumors. Will it work in human patients?

Multiple-drug resistance is usually considered a problem in cancer therapy, but some corporations see a way to turn it to the patient's advantage. Applied Immune Sciences in Santa Clara, Calif., has a system for separating stem cells—which can reconstitute the entire immune system—from bone marrow. By adding the gene for multiple-drug resistance to stem cells before reinfusing them, the company hopes to enable physicians to use greater quantities of chemotherapeutic agents, with fewer side effects,

courtesy of APPLIED IMMUNE SCIENCES

CELLS ARE TENDED by researcher at "cell therapy center" established by Caremark International and Applied Immune Sciences. Gene therapy trials are planned.

in patients who have received bone marrow transplants.

Even infectious disease might be tackled with gene therapy. Viagene in San Diego is gearing up for a trial in which patients are injected directly with a modified retrovirus that inserts particular HIV genes into a patient's cells. The company believes the result will be a strengthened immune response to HIV, the AIDS-causing virus.

Retroviruses are not the only possible vectors. Indeed, they have a major limitation: they can infect only cells that are dividing. Ronald G. Crystal of Cornell University may have solved that problem in cystic fibrosis patients by using an adenovirus to deliver a gene to the lung. Genzyme in Cambridge, Mass., is investigating both adenovirus and adeno-associated virus (AAV). Using adenovirus, the company says it has corrected the cystic fibrosis defect in the nasal cavities of three patients, a first step toward experiments in the lung.

Several corporations appear to be impressed with the virtues of AAV, including Targeted Genetics in Seattle, which is using it to stimulate HIV-fighting immune cells. Whereas retroviruses incorporate their genes into chromosomes at random sites, AAV integrates its cargo at specific sites; in theory, that should be safer. And AAV, unlike adenovirus, causes no known illness in people. Avigen in Alameda, Calif., is working on AAV systems for some of the most common genetic diseases: sickle cell anemia and thalassemia.

Others want to get away from viruses altogether. Vical in San Diego is one of several firms exploiting the surprising fact that DNA injected directly into the body can be taken up by some cells and expressed. The company has started trials to enhance the immune response of patients who have malignant melanoma, and it has announced a collaboration with Genzyme on cystic fibrosis. GeneMedicine in Houston is poised to start treating muscle wasting by direct DNA transfer. And Cell Genesys in Foster City, Calif., has ambitious plans to use so-called gene targeting to add receptors to human immune system cells so they can fight particular diseases. The cells would have patient-specific markers removed so they could be injected into anyone.

Despite the excitement, the trials now use only small numbers of patients and are aimed solely at establishing the feasibility of the approaches. Many therapies that have shown promise in early studies have failed to produce real benefits when tested in large numbers of patients. "We don't know if any one of these things is going to work," notes Ivor Royston, scientific director of the San Diego Regional Cancer Center.

True, but the business side of the house sounds bullish. "If some of these therapies work in the trials now under way, you could see product approvals within the next three years," observes Jeffrey R. Swarz, a biotechnology analyst at First Boston. "It's not as faraway as some people think."—*Tim Beardsley*

Bright Future

Porous silicon proves versatile, but is it real?

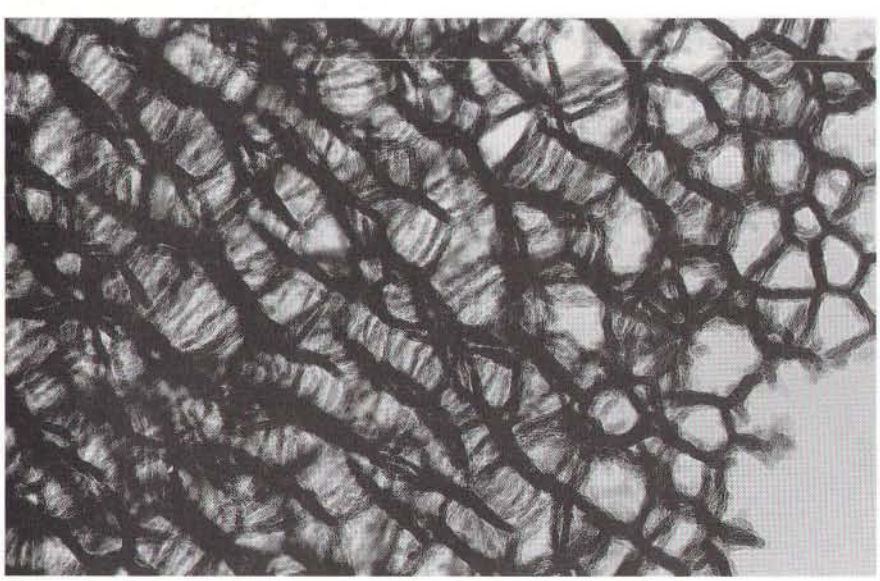
Leigh T. Canham knows of 14 different theories that explain why an etched silicon wafer that is 80 percent air glows orange under ultraviolet light. The same material can also emit red, orange, yellow or green under the influence of an electric field. Depending on which explanation turns out to be right, porous silicon could be the next electronic material for a myriad of applications or a quaint dead end.

Today designers who want to build circuits that meld electrons and light—such as optical computers or lasers for fiber-optic communications systems—must use exotic, fragile materials such as gallium arsenide. But if silicon can be made to emit light on a commercial scale, they will have a cheap, durable alternative backed by three decades of manufacturing experience.

Theories about silicon luminescence fall into one of three main classes. Canham, a physicist at the Defence Research Agency in Malvern, England, is one of those who champion the notion that the light is emitted by quantum wires or dots—essentially artificial atoms—that form when electrons are confined within the minuscule filaments of silicon left by the etching process. Electron micrographs show crystallites only a few nanometers across, containing perhaps 1,000 atoms.

Martin Rosenbauer and his colleagues at the Max Planck Institute for Solid State Physics in Stuttgart, in contrast, contend that the light comes from a surface layer of siloxenes (compounds containing silicon, oxygen and hydrogen) that forms during and after etching. And Frederick Koch's group at the Technical University of Munich, among others, is exploring the possibility that the emissions result from "surface states," peculiar energy levels created when most of the silicon structure is etched away so that many atoms no longer enjoy the "infinite" lattice of neighbors that marks a large crystal.

Koch and his co-workers have cast doubt on the siloxene model by heating samples briefly to more than 700 degrees Celsius; the rapid baking drives off all the hydrogen but does not materially affect the glow. He finds fault with the pure quantum confinement theory as well, however: some workers have seen strong luminescence from samples in which essentially all the silicon has been oxidized to silicon dioxide.



ANTHONY CULLIS *Defence Research Agency*

***SILICON MESH** seen in this electron micrograph is 92 percent empty space. Filaments of luminescent material are only a few nanometers across.*

In Koch's model, electrons and holes (the absence of an electron where one ought to be) trapped within the tiny crystallites migrate to the surface, where they recombine. Recombination inside a bulk crystal generally produces heat rather than light. But the strange conditions of the surface, partway between those of a molecule and a crystal, lead to arrangements of energy states that favor light emission, Koch says.

Both Canham and Koch agree that the ultimate explanation will probably incorporate elements of several models. "There is no quarrel about the observations," Koch says, "so the stories you make up about them are going to converge."

While the theorists and experimentalists are arguing over how porous silicon actually works, others are extending the range of what it can do. Jean-Claude Vial and his colleagues at the University of Grenoble, for example, have built light-emitting devices that can change the color of their glow from red to green depending on the voltage across them. Changing the electric field by fractions of a volt apparently stimulates crystallites of differing sizes, thus producing the various colors.

At the University of California at San Diego, a team headed by Michael J. Sailor is exploring the material's potential as a sensor: a whiff of ethanol vapor on the surface cuts luminescence by 97 percent. Other chemicals have a similar but less drastic effect.

Bringing such devices out of the laboratory will require dealing with some fundamental contradictions. For example, tiny crystallites emit light well, but they do not pass current. An electrical contact on top of a layer of porous silicon can excite only a fraction of its crystallites. Researchers use a liquid electrode to make contact throughout the porous silicon, but this is impractical for commercial use.

Experimenters are attempting to deposit layers of metal within the silicon matrix, to impregnate it with a conductive plastic or simply to make the silicon itself in such thin layers that only surface contacts are needed. Similarly, although a wide range of pore and column sizes could permit a light-emitting device to switch colors in a trice, digital-circuit designers may not be very happy with transistors that switch on or off at an uncontrollable range of voltages.

In any case, commercialization is still well over the horizon. "It's not a technology," says Bernard S. Meyerson of IBM. "It's got to be something more than what you can wipe off the surface of a chip with a Q-tip." —*Paul Wallich*

The Color of Sound

Shedding light on sonoluminescence

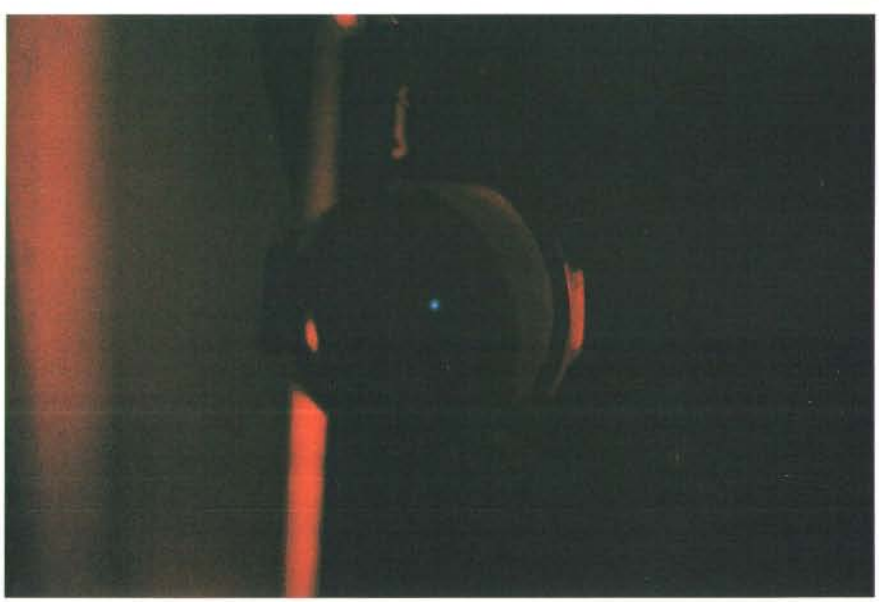
Converting sound into pulses of light might appear to be a stunt best left in unimaginative music videos. Yet it interests physicists, among them Seth J. Putterman. In his laboratory at the University of California at Los Angeles, Putterman and his students direct sound at a flask of water. The sound can cause an air bubble inside to emit flashes of blue visible to the unaided eye. Somehow sound energy is being concentrated by a factor of a million million to produce temperatures inside the bubble that exceed 10,000 degrees Celsius—far hotter than the surface of the sun. "It is an extremely robust and amazing phenomenon," Putterman remarks. "Where else in nature do you get a concentration of energy by 12 orders of magnitude?"

Experiments during 1992 and 1993 have done much to improve understanding of sonoluminescence. The effect was discovered in the 1930s, and the prevailing wisdom since then has been that the process must stem from acoustic cavitation—the growth and collapse of bubbles in water. It had long been known that such bubbles can collectively pack enough energy to pit ship propellers. If the bubbles collapse violently enough, a "hot spot" emerges, an area reaching about 5,000 degrees C. This energy excites molecules that later release photons.

But recent work by Putterman and others has cast the phenomenon in a new light, so to speak. Putterman studied a single bubble, a technique first demonstrated by Lawrence A. Crum, now at the University of Washington, and his colleagues. This setup produces a stably flashing bubble, so investigators can scrutinize the effect with much greater rigor than had been possible. Putterman uses a piezoelectric transducer—a small loudspeaker—pressed against a flask of water. The right combination of loudness and pitch creates and traps a sonoluminescing bubble. The radius of the bubble fluctuates with the oscillations of the sound frequency (typically about 25 kilohertz, just beyond the range of human hearing). It expands up to 45 microns and contracts down to less than a micron. The sound pressure exerted on the bubble would roughly translate to about 110 decibels if one could hear it, a level equivalent to the noise intensity from a jet engine a few meters away.

The surprising result: the flashes of light emerge like clockwork and last only a fleeting 50 trillionths of a second. "That turns out to be orders of magnitude shorter than the hot-spot theory predicts," Putterman says. Moreover, the photons emitted are concentrated in the violet and ultraviolet regions. "To get such photons, the system must be very hot," Putterman explains. "The temperature could be well above 50,000 degrees C." That level is a factor of 10 higher than that deduced with previous descriptions.

If conventional wisdom does not ex-



SETH J. PUTTERMAN

BACK IN A FLASH: blue light from an air bubble trapped in a flask of water pulses in time with the frequency of an external sound field.

plain the energy concentration, what might? One calculation, made earlier this year by Putterman's U.C.L.A. colleagues Cheng-Chin Wu and Paul H. Roberts, provides a plausible scenario: the bubble collapses faster than the speed of sound. The collapse creates a supersonic shock wave directed to the center. The imploding wave compresses the trapped gas so forcefully that the air is heated into a plasma, reaching above 10,000 degrees C. The key to the shock-wave scenario, Crum believes, seems to be the "exquisite symmetry" of the single bubble; the hot-spot theory of molecular excitations probably holds sway in situations in which the bubbles do not collapse symmetrically.

Sonoluminescence could even be more robust than results indicate. The temperature may go up to 100,000 degrees C. "The key challenge for 1994," according to Putterman, "is to determine how high in energy the photons go." Light of frequencies higher than the ultraviolet range does not propagate in water, so the researchers may be missing some photons. Putterman will be experimenting with fluids other than water and with gases other than air.

The physics of sonoluminescence also has a practical side. "If you could scale things up, you might be able to dump materials inside a luminescing bubble," Crum explains. The ultrahigh temperatures would easily break down toxic materials. The bubble may also produce exotic materials by providing an unusual environment for chemical reactions. Putterman is patenting certain aspects of his setup, because "it is a cheap picosecond light source," for use in fluorescence studies and in the calibration of detectors. —*Philip Yam*

Clean Definitions

The nation contemplates what to do with Superfund

The Clinton administration may begin to yearn for the fun of nominating Supreme Court judges or fashioning policy for Somalia as it tries to overhaul one of the most contentious environmental laws on the books—the 13-year-old Superfund law. (The administration was to present its proposals for Superfund renewal to Congress toward the end of November.)

One much highlighted aspect of the program is its liability provision. It holds that a few deep-pocket corporations can be forced to bankroll the cleanup of all the wastes deposited for decades in a landfill. That provision can and has triggered cascades of lawsuits as the parties named by the Environmental Protection Agency start litigating to collect from others who might have dumped at the same waste site.

But both environmentalists and many businesses believe the most important question to be addressed in the reauthorization process should be whether the Comprehensive Environmental Response, Compensation and Liability Act of 1980 (aka Superfund) is protecting public health at a cost society can afford. A central issue, raised throughout the program's history, is: How clean is clean? "Are we spending this money well, and what are we getting for it?" asks Katherine N. Probst, a fellow with Resources for the Future, a Washington, D.C.–based think tank. "These issues generate more costs for the program than people suing each other."

One of the early actions of Carol M. Browner, the EPA chief appointed by President Bill Clinton last winter, was to initiate the consensus-style of policy-making that has characterized the administration. She named an advisory committee on Superfund made up of industrialists, environmentalists, polluters and state officials, among others.

The nearly 1,300 Superfund sites range from graveyards for rusting barrels of used solvent to municipal landfills that contain tin cans and old trash mixed in with barely detectable traces of organic chemicals or lead. Industry groups charge that despite different levels of risk at various sites, the EPA favors the most draconian solutions: risk assessments that make worst-case assumptions that end in exaggerating threats to human health by a factor of 100 or 1,000 or more.

The Hazardous Waste Cleanup Project, a coalition of trade groups that encompasses organizations ranging from the Chemical Manufacturers Association to the American Insurance Association, cites the case of a former agricultural chemical-processing facility in the Southeast that despite being fenced and locked had to meet a cleanup standard that assumed a child was feasting on a constant diet of dirt. "Under certain circumstances it may be realistic to assume that a young child will breach site security and dig two feet underground to play in the most contaminated 'hot spot' at a hazardous waste site," a report from the group stated. "But that child is not likely to do so 350 days per year, as specified in the EPA's 'Standard Default Exposure Factors.'"

On the other side of the committee table are environmental groups like the Natural Resources Defense Council

ALEX QUESADA *Matrix*

HOW TO CLEAN UP a Superfund site, such as the one pictured here, is an issue in the renewal of the 13-year-old law.

(NRDC), who question whether Superfund has ever been given a chance to prove itself during two more or less unsympathetic administrations. In this argument, risk assessors may need the much-maligned worst-case scenarios to protect public health because of the margin for error that exists in estimating harm from sites contaminated with a witch's brew of chemicals. And protection of groundwater, not kids swallowing dirt, justifies the tendency to hew to conservative numbers.

An underlying problem, the NRDC says, is the absence of a cohesive set of national standards for groundwater and soil contamination. The multiyear process of site assessment often relies on a hodgepodge of sometimes conflicting state and federal laws. "What happens is that at every site we're reinventing the wheel," asserts Linda E. Greer, an environmental toxicologist with the NRDC. "We're having debates at one site after another about what levels of contaminants would be protective of human health, and they cause a tremendous amount of disagreement among all the affected parties."

Even if the risks can be adequately identified, the needed cleanup technologies may be lacking. A proved method has yet to be invented that can completely remove deposits of pollutants denser than water that concentrate in tiny globules in the soil—wood preservatives and chlorinated solvents, for example. The 1986 Superfund Amendments and Reauthorization Act (the only major revision to the law) directed the EPA, where possible, to call for treatment methods that could permanently dispose of toxic wastes.

But the technology available for some types of cleanup has met with a decidedly mixed reception, both from technocrats and the public. WMX, the nation's largest waste management firm, announced layoffs of 1,200 employees in one of its divisions in late September because of lower than anticipated demand for its services. This happened, in part, because incineration technology met with opposition from a public afraid of burning chemical residues. "We made a large capital investment in incineration capacity," says Sue Briggum, a government affairs representative for WMX. "It turned out to be vastly underused."

Superfund does have an internal program to evaluate new technologies. It consumes just about 1 percent of Superfund's primary source of funding, which comes from a $1.7-billion tax on chemical and petroleum producers as well as other industries. The EPA has developed a data base on bioremediation, and it wants to help organize an "eat-off" to test the effectiveness of different microbes. But development of cleanup technologies often proceeds slowly. As often as not, early prototypes frequently run into problems.

Some industry organizations believe part-per-million cleanliness, desirable for a schoolyard, is overkill at enclosed and abandoned industrial sites. Where there are no immediate threats to public health, the treatment provisions of the 1986 revisions in the law, they say, should be changed to encourage waste containment, not treatment. "Something like dioxin isn't going anywhere," says Bernard J. Reilly, corporate counsel for Du Pont. "You can keep it in place for a couple of million dollars, or you can burn it for $100 million."

But as time passes, the NRDC claims, containment measures are bound to come undone. The advocacy group also worries that those liable for the cleanup will try to slop clay over a landfill and then walk away for good. It has proposed to the EPA that when a containment strategy is employed, the companies responsible should pay money into a fund that would be used to finance new technology development. The EPA would be required every five years to evaluate whether technology had become available to finish a cleanup. If it had, then the polluter would have to go back and finish the job.

Whatever path is taken, the bureaucratic process will trickle along like groundwater. Eight to 10 years now elapse before the site evaluation process is completed and a cleanup begins, although emergency cleanups of chemical spills and contaminants are a lot quicker (the agency has completed 3,200). Even by government standards, though, the longer-term cleanup process has moved slowly, which has become another issue in the debate about overhauling the program. As of the end of September, the agency had finished work at only 217 of nearly 1,300 sites on the Superfund list. The average cost has been $27 million a site. Two thirds of the sites listed by the EPA as complete still need ongoing care—pumping and treatment measures, for example.

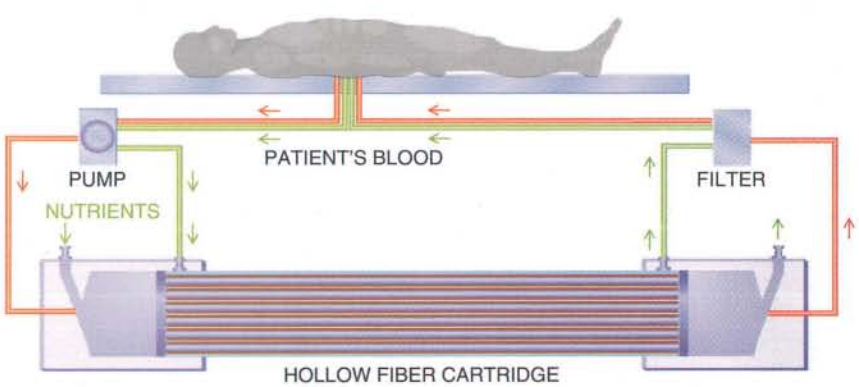
So why not just scrap things and start anew—a question that might well occur to Bill Clinton and Carol Browner? Perhaps the main reason for not getting rid of Superfund is that any offspring would probably take another 13 years to get going. Then it would be time to draft another bill. For the time being, the only people who clean up are the lawyers. —*Gary Stix*

Deliverance

Medicine closes in on an artificial liver device

Over the past half century, doctors have devised machines that can do the work, for a time, of nearly every vital organ in the body—with the notable exception of the liver. For the roughly 40,000 patients in the U.S. whose lives are threatened every year by liver failure attributable to disease, poisoning or infection, there has been only one alternative: a human liver transplant. Other options are at last coming into reach, in the form of living machines called external liver-assist devices (ELADs). At least five different devices are likely to enter human clinical trials next year.

The liver has defied imitation for so long because it is one of the most biochemically complex organs, responsible for manufacturing enzymes, bal-



***ARTIFICIAL LIVER** devices typically pump blood through porous tubes surrounded by liver cells* (red circuit). *Another option is to put the cells inside the fibers and feed them nutrients; blood then flows in the space between the strands* (green circuit).

ancing hormones, storing sugars and vitamins, and detoxifying the blood. Whereas mechanical contrivances can, in a pinch, stand in for a failed heart, lung or kidney, the sole entity that can do a liver's work is a liver cell, the hepatocyte. The primary challenge in creating an artificial liver device is thus to gather a large, dense and healthy enough population of hepatocytes outside the body to provide respite for the dying liver inside.

The simplest ELADs in commercial development are based on kidney dialysis machines. W. R. Grace's design is typical. A bundle of hollow fibers made out of a filterlike membrane is put in a canister. Pig hepatocytes coat the outside of each fiber. As a patient's blood is pumped through the inside of the fibers, the blood and the living cells exchange nutrients, toxins and other small molecules through the fiber walls.

The tricky part is sustaining the cells long enough to be useful and cost-effective—hepatocytes are loath to grow in vitro. Grace has published little about its technique, leaving many to wonder how or whether it has managed to accomplish this.

Other researchers have had to take further steps to address the problem. Cellex Biosciences, for example, reversed the traditional dialysis design in its ELAD. Rat hepatocytes are packed inside the hollow fibers and fed by a stream of supplemental nutrients while blood runs through the gaps between the strands. A richer diet should make the liver cells work more efficiently, Cellex reasons, requiring less blood to be tapped from the patient. If the company is correct, its device might be easier on weak patients than are other designs.

Cellex claims its ELAD can sustain liverless rabbits for 36 hours. Presuming that a controlled study with dogs goes well this fall, its ELAD, the development of which Cellex recently spun off into a new company called Regenerex, could see human trials next summer. Scaling the device up to human proportions may, however, prove technically daunting.

Achilles A. Demetriou, a surgeon at Cedars-Sinai Medical Center in Los Angeles, worries that clotting might also prove to be an obstacle. Most liver-assist devices require the use of heparin or a similar anticoagulant to ensure smooth circulation through the device. "These patients already have massive bleeding disorders," Demetriou points out. Heparin could make them worse.

He is testing a different kind of ELAD that avoids clotting problems—and the need for heparin—by first separating plasma out of the patient's blood. Demetriou's device pumps just the plasma through the canister, which contains pig hepatocytes, and then through an activated-charcoal filter before adding back the cellular portion and returning the reconstituted blood to the patient.

Cedars-Sinai's design, though by far the most complicated liver machine yet tried on humans, can nonetheless claim the best track record. Demetriou says that of 10 patients he has put on the device—most of whom were so near death that they were disqualified from receiving a transplant organ—eight recovered enough to receive a new human liver and to go home.

The surgeon would like to use the device on 10 more patients before beginning a large multihospital study sometime next summer. Until such a controlled trial is completed, doctors cannot know for sure whether animal hepatocytes can safely and effectively stand in for a human liver. "There are not many significant qualitative differences between rat, dog, pig and human hepatocytes," Demetriou asserts. But there are many quantitative differences, and researchers agree that human cells would be ideal, if only they could be grown in the lab.

At least two companies have been able to do just that. Hepatix was founded three years ago by two physicians at the Baylor College of Medicine who managed to isolate from a human liver tumor a line of hepatocytes that thrives in vitro. When planted in a modified kidney dialysis canister, a few grams of the cloned cells will grow to fill the available space, in four weeks reaching 200 grams—10 times the amount of pig cells used in the Cedars-Sinai device.

Except for their growth rate, "these cells act virtually exactly like human hepatocytes," claims Phillip C. Radlick, Hepatix's president. But the cells' cancerous origin makes some researchers uneasy. A closely related strain has been shown to form tumors in mice. Although there is little risk of the cells themselves getting into the blood, some cancers are caused by viruses, which could cross the protective membrane. That prospect bothers Demetriou. "These patients will have to be immunosuppressed for life if they receive a transplant," in order to prevent rejection. That makes them especially vulnerable to pathogens, he observes.

Hepatix is betting that the risk of inducing tumors is minimal and is outweighed by the ELAD's immediate medical benefit. But that, too, has yet to be proved. So far 11 patients have used the device. "We had 100 percent success with regard to safety," Radlick boasts, "and we got very good metabolic support—enough to encourage us very strongly to go into large-scale trials and to go for market release in Europe." Only one of the patients survived, however.

Hepatix may soon have to contend with a formidable competitor as well. Advanced Tissue Sciences, which specializes in culturing human tissues, has recently formed a separate business unit to focus on artificial livers. Bernard D. King, who heads the project, claims his researchers have found a way to grow substantial masses of normal human liver tissue. The firm is preparing to apply for a patent on its bioreactor, which uses a three-dimensional framework of nylon screens or biodegradable polymer meshes to support the liver cells as they divide and differentiate. King predicts that the company's ELAD based on normal human hepatocytes will enter pivotal preclinical studies in animals early next year. Eventually, he says, "we dream about pulling out someone's liver and putting in something that we've grown."

As artificial livers emerge into common medical use, they raise difficult ethical issues. To date, experimental ELADs have been used almost exclusively to sustain patients until a human organ is available and the patient is strong enough to survive transplant surgery. But, observes John Logan, a vice president of DNX, "if a device is just a bridge to transplant, then it's a bridge to nowhere, because there aren't enough organs available." Last year there were just 3,059 human livers to ration among approximately 15,000 people in the U.S. who needed a transplant. The gap grows wider every year.

Is it ethical to deny a liver to someone who has cirrhosis in order to transplant it into a hepatitis victim who would have died but for an artificial liver device? After all, the hepatitis victim may recover spontaneously, whereas the cirrhotic patient almost certainly will not. On the other hand, is it ethical to refuse to put a dying patient on an ELAD when there is a good chance that she will revive only enough to require a new liver?

"Someday we'll be transplanting animal organs into humans, and it won't be an issue any longer," says Jeffrey L. Platt, a surgeon at Duke University Medical Center. Indeed, DNX announced in October that it had developed a transgenic pig whose organs are protected from attack by human antibodies, cracking open the door to xenotransplantation. That solution is still years away, however. In the meantime, researchers must strive to make artificial liver support a viable and reliable treatment in its own right. —*W. Wayt Gibbs*

Fractured Functions

Does the brain have a supreme integrator?

The brain, as depicted by modern neuroscience, resembles a hospital in which specialization has been carried to absurd lengths. In the language wing of the brain, some neurons are trained to handle only proper nouns, others only verbs with irregular endings. In the visual-cortex pavilion, one set of neurons is dedicated to orange-red colors, another to objects with high-contrast diagonal edges and still another to objects moving rapidly from left to right.

The question is how the fragmentary work of these highly specialized parts is put together again to create the apparent unity of perception and thought that constitutes the mind. This puzzle, known as the binding problem, has loomed ever larger as experiments have revealed increasingly finer subdivisions of the brain.

Some theorists have suggested that the different components of perceptions funnel into "convergent zones," where they become integrated. Among the most obvious candidates for convergent zones are regions of the brain that handle short-term, or "working," memories so that they can be quickly accessed for a variety of tasks. Yet two different sets of experiments done this year—one in which monkeys were monitored by electrodes and the other in which humans were scanned with positron emission tomography (PET)—show that the parts of the brain that cope with working memory are also highly specialized.

The monkey experiments were performed by Fraser A. W. Wilson, Séamas P. Ó Scalaidhe and Patricia S. Goldman-Rakic of the Yale University School of Medicine. The workers trained the monkeys to accomplish two tasks requiring working memory. In one task, each monkey stared at a fixed point in the middle of a screen while a square flashed into view at another location on the screen. Several seconds after the square disappeared, the monkey would direct its gaze to the spot where the square had been.

The other task required storing information about the content of an image rather than its location. The investigators flashed an image in the center of the screen. Each monkey was trained to wait until the object had disappeared and then turn its eyes left or right, depending on what type of object it had observed. Electrodes monitored the firing of neurons in the monkey's prefrontal cortex, a sheet of tissue that cloaks the top of the brain and has been implicated in mental activities requiring working memory.

In each test, a set of neurons started firing as soon as the image flashed on the screen and remained active until the task had been completed. But the "where" test activated neurons in one region of the prefrontal cortex, whereas the "what" test activated neurons in an adjacent but distinct region. "The prefrontal cortex has always been thought of as a region where information converges and is synthesized for purposes of planning, thinking, comprehension and intention," Goldman-Rakic says. "We've shown that this area is just as compartmentalized as the sensory and motor regions."

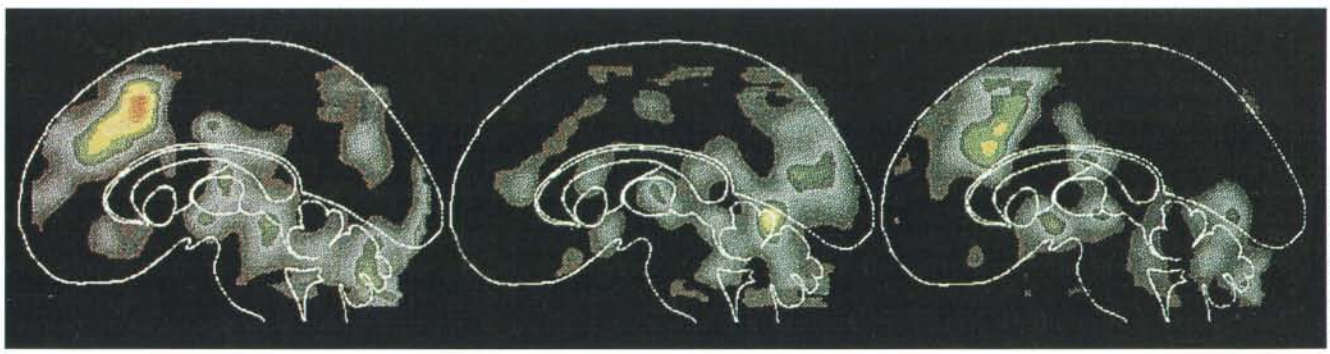
Complementary findings described this year by investigators at Washington University have emerged from PET scans of humans. (PET measures neural activity indirectly by tracking changes in blood flow in subjects injected with a short-lived radioactive tracer.) In the experiments, volunteers were provided with a list of nouns. They were required to read the nouns aloud, one by one, and to propose for each noun a related verb. On reading the noun "dog," for example, the volunteer might suggest the related verb "bark."

When the subjects first did this task, several distinct parts of the brain, including parts of the prefrontal and cingulate cortex, displayed increased neural activity. But if the volunteers repeated the task with the same list of nouns several times, the activity shifted to different regions. When the volunteers were given a fresh list of nouns, the neural activity increased and shifted back to the first areas again.

The experiment suggests that one part of the brain handles the short-term memory requiring verbal invention and that another part takes over once the task has become automatic. In other words, memory might be subdivided not only according to its content but also according to its function. "Our results are consistent with Goldman-Rakic's ideas," comments Steven E. Petersen, a member of the Washington University team.

So how do all the specialists of the brain manage to work together so smoothly? Are their activities coordinated by a central office or through some form of distributed network? Petersen favors "a localized region or a small number of localized regions," where perceptions, memories and intentions are integrated. Goldman-Rakic is leaning toward a nonhierarchical model in which "separate but equal partners are interconnected, communicating with each other."

Larry R. Squire, a memory researcher at the University of California at San Diego, thinks the binding problem may take many years to solve. He concedes that "we still don't really have a clue" as to what the binding mechanism is. But he is hopeful that the answer will inevitably emerge, given the rapid advances in techniques for studying the brain—



WASHINGTON UNIVERSITY

PET SCANS done at Washington University show certain regions of the brain engaged as a subject reads a list of nouns and suggests related verbs **(left).** ***Different regions become active after the task is performed repeatedly with the same list*** **(center).** ***The original areas of the brain are reengaged when the subject is given a list of new nouns*** **(right).**

including microelectrodes, noninvasive imaging technologies (such as PET and magnetic resonance imaging) and computers, which can help make coherent models out of empirical data. "We need it all," Squire says. —*John Horgan*

Core Questions

Glaciers and oceans reveal a mercurial climate

Discussion of whether human economic activity can affect the climate has generally rested on a comforting assumption: if change did occur, it would occur gradually. There would be time to respond. That assumption has been made untenable by analysis of glacial ice as well as of sediments from the ocean floor.

The findings reveal that far from being stable, the earth's climate has always changed quite abruptly—both during times of glaciation and, as the newest studies indicate, during interglacial periods such as the current one. "These are very exciting results," says M. Granger Morgan of Carnegie Mellon University. "Changes took place over shorter time scales than people had expected."

The ice core results come from the efforts of two teams of researchers, one European and one American. Five years ago they set out to find information that would create a more complete record of climates past. The groups selected locations 19 miles apart on the Greenland ice sheet. The European team finished their work in 1992; the Americans finished this summer. The cores they drilled and recovered sampled the ice and snow to a depth of 10,013 feet, encompassing a 250,000-year span of climatological history. (In another venture, Russian scientists are drilling in the Vostok site on the Antarctic ice sheet, hoping to capture at least 500,000 years of evidence.)

The unexpected picture of climate that has emerged from these cores has been reported in a series of articles in *Nature*. The European group—the Greenland Ice-Core Project, or GRIP—found that the last interglacial period, called the Eemian, was characterized by the sudden onset of cold periods that lasted for decades or centuries.

Although such vacillations had been observed in data from glacial times, finding them in the Eemian is significant because the climate was, on average, only a few degrees warmer than it is now. The studies "have concluded that 130,000 years ago, when the earth was as warm as it is today, there were very rapid changes from warm to cold climates," explains Michael L. Bender of the University of Rhode Island. "If that conclusion stands up, it is going to be extremely important because the very stable climate that the earth has had for the past 10,000 years will not necessarily stay that way."

The U.S. team—the Greenland Ice Sheet Project II, or GISP2—finished drilling six months after the Europeans. GISP2 has also documented rapid and dramatic climatic fluctuations. "That is the importance of having two cores," remarks Scott J. Lehman of the Woods Hole Oceanographic Institution. Because of compression and different characteristics of the ice, "it'll be interesting to see any corroboration," Lehman says.

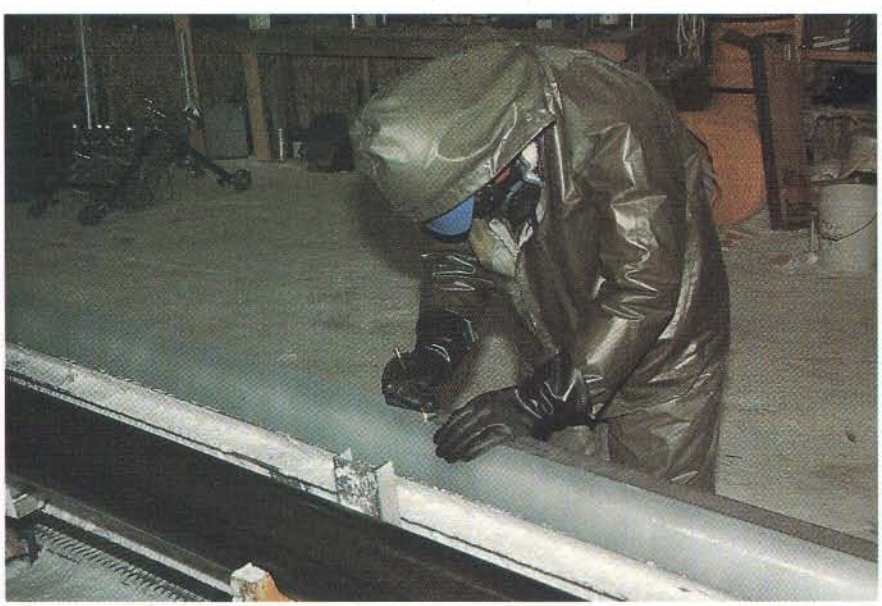
Marine sediment cores, taken by oceanographers, have supported the GRIP and GISP2 findings. By examining the presence of plankton that thrive at various temperatures, Lehman, Gerard Bond of Columbia University's Lamont-Doherty Earth Observatory and other researchers have been able to chart changes in temperature in the North Atlantic. The various groups have reported that the temperature record of the ice is echoed by the seafloor, suggesting that there are links between the temperature changes in the ocean and in the atmosphere.

The factors that cause the abrupt changes remain obscure. One theory holds that the heat-carrying capacity of the Atlantic Ocean—described as a conveyer belt—is somehow altered as fresh water is released by melting ice. These changes cause and are caused by changes in climate. Another hypothesis suggests that the conveyer is disrupted by global variations in rainfall.

For now, climate modeling is likely to offer only limited help in clarifying the reasons for the dynamic change. Although most models have found that doubling of carbon dioxide will result in a global temperature increase of 1.5 to 4.5 degrees Celsius, they are far from being able to incorporate all aspects of the climate system. "We are barely able to model the oceans; we cannot yet couple them with atmospheric models," Lehman says. Without a good model of these interactions, "the possibility of sudden changes is explicitly not allowed." Lehman goes on to note that one or two models have tried to include both elements: "And what do we get in them? Surprises."

So the Greenland findings, in sphinx-like manner, continue to pose questions. Were the changes local or global? If rapid fluctuations are the norm, why is the contemporary climate so stable? Could the accumulation of greenhouse gases trigger a dramatic, and potentially devastating, oscillation today?

"It is the biggest event this year," says Andrew J. Weaver of the University of Victoria in British Columbia, of the Greenland results. "The fact that interglacials are not times of stable climate," Bond adds, "is a warning that we are poised between modes and could bring on a switch." —*Marguerite Holloway*



MARK TWICKLER Glacier Research Group, University of New Hampshire

ICE CORE from Greenland indicates to researchers that climate has always shifted rapidly, even during the supposedly stable periods—such as the present one—that have existed between glacial epochs.

Living Legend

Is the last ground sloth hidden in the Amazon?

Brazilian lore has it that a red-haired, human-sized creature with a soul-wrenching scream lurks in the shadows of the rain forest. Amazonian scientists generally counter that this auburn yeti lurks only in the shadowy imaginings of rain-forest peoples. But one researcher has recently suggested that there may be substance to the myth—in the form of the planet's last remaining, or perhaps just recently extinct, ground sloth.

After eight years of gathering first-hand accounts of sightings of the animal, David C. Oren of the Emílio Goeldi Museum in Belém, Brazil, has published a monograph urging his colleagues to take tales of the mysterious *mapinguari,* as it is called in Portuguese, more seriously. Based on the narratives that he has collected, Oren postulates that the *mapinguari*—which has been alternately dismissed by researchers familiar with the stories as a primate or an Andean bear wandering off course—could be a ground sloth.

Ground sloths, some the size of elephants, first appeared more than 30 million years ago and were prevalent in North and South America as well as in the Caribbean. (A soon-to-be published study also documents fossils of ground sloths in Antarctica.) The mammals became extinct between 11,000 and 8,500 years ago. "They practically died yesterday," explains Malcolm C. McKenna of the American Museum of Natural History in New York City, which has a large collection of ground sloth memorabilia—including a sample of dung with a note attached to it that reads "deposited by Theodore Roosevelt." The two kinds of sloths that exist today, the two-toed and the three-toed tree sloth, are each related to a different ground sloth, McKenna notes. They are restricted to tropical Central and South America.

Oren, an ornithologist and expert on Amazonian biodiversity, says descriptions of the *mapinguari* offered by forest-dwelling peoples from widely different parts of western Amazonia resemble one another. These details are, in turn, consistent with characteristics gleaned from fossilized remains: red hair, tough skin (except around the navel), a loud cry and hind feet turned backward. *Mapinguari* tales become more fanciful in eastern Amazonia, Oren says. They include stories that the nocturnal creature has at times twisted off the head of a human and walked away with the decapitated corpse under one foreleg.

Because deforestation is less rampant in parts of the western region, Oren suggests that the ground sloth, if it existed or if it exists, is more likely to have survived there. Indeed, fossil remains of at least eight genera of ground sloths have been unearthed in the Brazilian state of Acre, which borders Peru and Bolivia. If the creature, or a fresh carcass of one, is found, Oren says, it will be further evidence that scientists should incorporate indigenous knowledge into their work on biodiversity.

McKenna admits that the *mapinguari* may well fall into the category of the Loch Ness monster. But he adds that a big mammal—the *Pseudoryx nghetinhensis* antelope of Vietnam—remained hidden from scientific scrutiny until it was discovered last spring. "If you are really cautious, you end up being a stick-in-the-mud," McKenna points out. One must also be careful not to lose one's head. —*Marguerite Holloway*

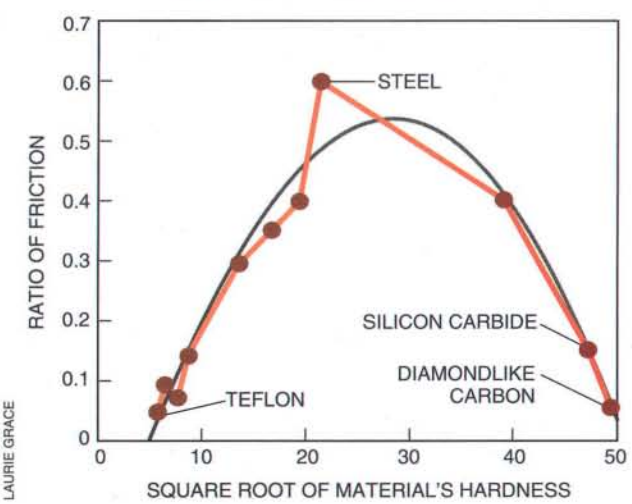
A Girl's Best Friend

Diamond continues to resist efforts at economic synthesis

Scientists and starlets alike seem dazzled by diamonds. This form of carbon constitutes both the most coveted jewel and the hardest, most thermally conductive material. For nearly 40 years, engineers have tried to exploit these properties. The crowning accomplishment would be to make synthetic diamonds and diamondlike materials more affordable for a range of commercial uses, from coating razors to creating computer chips.

Serious efforts are considered to have gotten under way in 1955, when scientists at General Electric formed what they thought was the first synthetic diamond. In fact, these same GE researchers recently announced new findings that show their gem was not man-made. Evidently, a fragment of natural diamond seed slipped into their sample. Nevertheless, the process was correct and eventually enabled them to synthesize the material successfully.

"The main limitation is that it's difficult to make diamond of high quality cheaply enough," says John C. Angus, professor of chemical engineering at Case Western Reserve University. Chemical vapor deposition, still the least costly method to apply a diamond film, produces at best an irregular quiltlike cover of carbon compounds; few patches resemble the crystalline structure of the natural gem. Some investigators have tried another tack, developing materials that have properties rivaling those of diamond. Diamondlike, noncrystalline carbon structures cannot yet match the physical properties of diamond. On the other hand, such materials cost less and can be applied to surfaces at low temperatures.



***VARYING AMOUNTS OF FRICTION** are generated by sliding soft, hard and superhard materials against unlubricated steel. The graph suggests that much harder diamond coatings may not offer much lower friction levels than cheaper diamondlike coatings.*

In recent months, journals and the popular press have celebrated several reports of the confection of cheaper synthetic diamond recipes and of the creation of harder, diamondlike materials. In June a Pennsylvania State University group announced their discovery of an inexpensive method for forming diamond films from a commercial polymer using a conventional oven. A month later Harvard chemists described a means for concocting a material, β-C_3N_4, they claim is actually harder than diamond.

The Harvard statement had

prepublication support. Marvin L. Cohen, a materials scientist at Lawrence Berkeley Laboratory, had predicted that this crystal compound of carbon and nitrogen atoms would be harder than diamond if it could be formed.

"Both these claims need to be independently confirmed, although they are potentially important," Angus says. "The field has been oversold," he adds, "but the potential hasn't been. The development is just going to be longer and more difficult than people think."

As the patent applications have piled up, other scientists have criticized the outpouring of papers as mere marketing. "The word 'diamond' sells," says Rustum Roy of Penn State. "There has been slow and steady progress but no breakthroughs." Nevertheless, market expectations are mounting. Workers at Microelectronics and Computer Technology Corporation in Austin, Tex., discovered earlier this year that thin synthetic diamond films emit a heavy shower of electrons when subjected to a weak electric field. In October top industry investigators formed a consortium to design flat-panel display screens that exploit such newfound electrical properties of the films.

In August, at the Applied Diamond Conference in Saitama, Japan, engineers from leading car companies presented papers on possible applications of diamond-film technology in the automobile industry. For example, a team at Michigan State University, supported by Ford Motor Company, is exploring ways to use synthetic diamond films to form simple circuitry, such as sensors that can function in hot, corrosive environments. They are testing similar films for coating factory tools to decrease wear, remarks Michael A. Tamor of Ford Research Laboratory.

Although they cannot resist wear as well as diamond films do, amorphous, diamondlike films are being tested as a coating for such sliding engine parts as pistons, Tamor reports. These films withstand nonabrasive wear so well that engineers can use lighter materials for a substrate. The resulting weight reduction translates into lower friction, higher mileage, lower emissions and greater overall cost-efficiency, Tamor notes. "In five years, we'll know if it's of any value, but it looks very promising," Roy says of the automotive research.

Lorelei Lee had no trouble making up her mind about diamonds, but the same cannot be said for Angus and other workers in the field. "Diamond has the best properties," Angus concludes. "It will find applications, but for some purposes, diamondlike materials may be better." —*Kristin Leutwyler*

When Cells Divide

Making space for the next wave of wireless communications

If Benjamin were in Westwood lounging around his parents' pool today, the word whispered in his ear would be "wireless." The wave that has rapidly but calmly lifted radio telecommunications from a niche technology to an $8-billion, 11-million-customer industry in just 10 years is starting to break. It has met another wave: the swell of digital networks as computers evolve from tools of calculation to portals of communication. Caught in the spray, cellular companies are thrashing about to get atop this confluence.

For the industry to thrive, it must simultaneously become more competitive and more cooperative. Simply lowering the price of admission to wireless networks is not enough; the diverse equipment and services must all work together as well. With the right balance, the wireless market could quintuple in the U.S. over the next decade, predict market analysts at Arthur D. Little. That event would bring personal, portable telephone services to 60 million people and their computers by 2005.

Substantial technological hurdles must be cleared if that is to happen. The first is capacity: the analog radio infrastructure in place simply does not have enough channels to support an explosion of demand. The FCC's decision in September to auction off 160 megahertz of bandwidth for personal communications services—more than three times the portion of the spectrum currently allotted to cellular telephone systems—is but a temporary fix. For the FCC also decided to allow existing mobile telephone companies to purchase only small plots of that valuable real estate; the rest will go to new entrants, up to seven per city.

As the resulting competition drives prices down, rising consumer expectations seem likely to force capital investment up. In order to entice customers not reared on the fuzzy, unreliable connections typical of the analog Advanced Mobile Phone Service (AMPS) standard, cellular companies must be able to offer not only land-line-quality speech transmission but also reliable connections for a new breed of fast computer modems.

Indeed, as Benjamin L. Scott, chief operating officer for Bell Atlantic Mobile, notes, "the growth potential for wireless data service is enormous. In our markets alone, $1.3 billion is up for grabs." Cellular firms realized long ago that to meet all these demands, they would have to replace AMPS with a digital standard. The prospect of being trapped with shrinking margins and no way to add customers has simply added a note of urgency to the debate over what that standard should be.

In its rush to develop digital services, however, the cellular industry has made several false starts. GTE Mobilnet and Ameritech, among others, have announced with much fanfare a service they plan to offer next spring: Cellular Digital Packet Data. By stuffing chunks of your data into the pauses in other people's conversations, the service should provide wireless connection to the Internet at speeds up to 19,200 bits per second. But if all-digital wireless service is introduced over the next two years as expected, such analog-based services will succumb to obsolescence.

The cellular industry's first attempt at a digital standard may suffer the same fate. The Telecommunications Industry Association adopted a scheme called Time Division Multiple Access (TDMA) in 1989. TDMA increases the capacity of analog cellular systems up to six times by chopping conversations into short segments and interleaving pieces from several conversations into each digital channel.

Ten large cellular telephone companies signed on as early adopters of TDMA. But within a year the standard was challenged by a rival method proposed by Qualcomm, a San Diego startup. The company had patented a technique called Code Division Multiple Access (CDMA), which it claimed could increase by 10 to 20 times the capacity provided by AMPS, while delivering better quality than TDMA.

Qualcomm tries to do this by avoiding the use of channels. Instead CDMA dumps all the transmissions sent within a cell into one wide band. It keeps individual signals separate by assigning each one a computer-generated code. That code is then used to manipulate data or digitized speech mathematically so that its bits are spread evenly throughout the spectrum, where they mingle with bits from up to 61 other conversations. A base station, portable telephone or laptop modem receiving a CDMA call can use the same code to unscramble an incoming message. All other transmissions, scrambled with different codes, look like ordinary static to the receiver and are filtered out.

By reducing interference to incoherent noise (as opposed to a coherent conversation), CDMA can use the same wide band of spectrum in every cell.

TDMA and AMPS, in contrast, must carefully assign channels so that no frequency is ever used in two adjacent cells. Aside from wasting spectrum, this forces a caller's telephone to switch channels abruptly when she crosses a cell boundary. Such hand-offs are the main source of dropped calls. With no channels to switch, two CDMA base stations can talk to the same telephone at once, allowing "soft" hand-offs. And because CDMA systems can fill the spectrum with more information, they can accommodate more callers.

Qualcomm has tacked other innovations onto its standard to boost capacity further. Whereas TDMA always digitizes speech by sampling it 8,000 times per second, CDMA uses a variable-rate digitizer that sends just 1,000 bits per second during the 60 percent of a typical conversation that a person spends listening or thinking. The extra airwaves can be used by other calls. A so-called rake receiver turns the bane of radio communications, multipath distortion, to its advantage. The problem occurs when a signal, having bounced off buildings or hills, arrives from several directions at slightly different times. In television, this problem causes ghost images. The rake receiver watches for such reflections, picks the three strongest and combines them to produce a clearer signal. Finally, built-in power control lets base stations instruct portable telephones to turn their transmission power up or down to avoid fading out of range or overwhelming other signals.

It took three years of testing, but Qualcomm finally convinced the industry to canonize CDMA as a second digital standard this past July. The technique has steadily gained support since, garnering commitments from three of the biggest cellular service providers, with another three expected to sign up soon. U.S. West has begun installing CDMA equipment in the Seattle area, according to a company spokesperson, and plans to offer the service to customers late next year. Yet the majority of carriers are not expected to go digital until well into 1995.

By that time, observes Gregory Pottie, a wireless technology researcher at the University of California at Los Angeles, the state of the art may have advanced considerably. "I think there is another factor of four or five to be gained in capacity" above what CDMA promises, he says. Clever use of multiple antennas in each telephone can reduce distortion, for example. Engineers at U.C.L.A. and the Georgia Institute of Technology are testing improved coding schemes that adapt to changing interference conditions to help reduce errors. And AT&T is working on advanced speech-compression algorithms to halve the amount of data needed for land-line quality.

Longer-term gains may come from research into ways of canceling out interference altogether. "The base station is receiving signals from every user anyway," Pottie points out. "Why shouldn't it process this information to wipe out unwanted interference between callers?" This need not require a supercomputer, he asserts. "Typically, there are a few users who dominate the interference; you cancel just the worst offenders."

Combined thoughtfully, these innovations could open enough airspace for 150 million wireless customers in the U.S., Pottie estimates. If the cellular industry can draw half that many away from traditional copper-wire telephone companies and future optical-fiber and coaxial cable services, it will have done well for itself indeed. —*W. Wayt Gibbs*

Shrinking Sandbox

IBM's woes visit its esteemed research division

It was as inevitable as autumn. The researchers who fill the laboratories and debate in the hallway carrels spotted throughout the curved glass temple of basic research designed by Eero Saarinen for IBM in Yorktown Heights, N.Y., have begun to feel the chill emanating from the downturn in the corporation's fortunes.

At Yorktown Heights—the Thomas J. Watson Research Center—as well as at IBM's Almaden and Zurich research laboratories, the total complement of researchers in the physical sciences will have fallen from 330 to 220 by the end of 1993, all through retirements or transfers to other jobs. Since 1991, the research division as a whole, which also includes computer science and other more applied research, has dropped by 600 individuals to 2,600, the first major cutback in its nearly 50-year history. "A lot of people doing the best research picked up and left," says Matthew P. A. Fisher, a well-known condensed matter theorist who moved to a research job at the Institute for Theoretical Physics at the University of California at Santa Barbara earlier this year.

Unless IBM's fate worsens, survival of the laboratories is not at stake. Except for small additional cutbacks next year, the contraction has stopped. Fears about Louis Gerstner, IBM's chief executive famed for his surgical cost cuts at RJR Nabisco, have abated. Gerstner apparently has no plans to carve the company into separate units, which could cast doubt on the future of a central research laboratory.

The research division, in fact, suffered less than the rest of the company, which experienced more punishing cutbacks. "We're in a different state than we were in the early part of the year when there was a great deal of uncertainty about the continued existence of the research division," says Daniel J. Auerbach, a manager at the IBM Almaden Research Center in San Jose, Calif.

Yet uncertainty persists about the preservation of a culture carefully nurtured since IBM's first laboratory opened on the campus of Columbia University in 1945. It is a culture that has produced Nobel Prizes for researchers for two discoveries—the scanning tunneling microscope and high-temperature superconductivity—and contributed mightily to progress in physics, mathematics and computer science.

Researchers worry about the disappearance of the "sandbox," the playlike pursuit of an idea that may or may not lead to an invention or a theoretical insight. Yet not everyone shares the view that IBM research was inviolable. By some accounts, the shakeup was overdue. "There was a group of people who felt they were special people and should do research in any area they chose," says Grant Willson, a former manager in polymer science at the Almaden Center. "They weren't doing world-class stuff. They would do something, and they would go to a society meeting where the size of the meeting was 150 people, and they would give each other prizes and praise each other and then go back and do it some more."

Responsibility for the corporation's inability to perceive a changing market has not been blamed on the research division. It is generally conceded that upper management, headquartered a few miles away in Armonk, failed to listen to entreaties from research management about the value of new technologies, such as John Cocke's high-speed reduced-instruction set computer chips. But research should have done better, says its current manager. "I think at that time we were not sufficiently aggressive in doing what it took to succeed," laments James C. McGroddy, director of the research division.

The recent upheavals have accelerated the linking of the work of the laboratories more closely to that of the corporation, a process that began more

than a decade ago. The shrinkage in physical sciences was not mirrored in the computer science department within the division. Dressed in a striped shirt, absent tie or jacket, McGroddy explains why. He points to a series of stacked rectangular boxes he has scribbled on a blackboard in his office. The box at the bottom represents atoms and electrons, with semiconductor chips and other hardware one box up.

But McGroddy gestures toward the top layer, labeled "customer solutions," an amorphous category that represents the need to bring together software, hardware and expertise for the information-processing needs of, say, a motor vehicle bureau. "The intellectual challenges, in many cases, moved up into this region," McGroddy says. "And they don't fit well with the traditional things that universities have done and the things that [corporate] research laboratories have done."

The IBM research division plans to expand its software and consulting—what McGroddy calls services, applications and solutions—from 12 to 20 percent of the division's budget. The division's expenditures are now about $450 million, which is some $50 million less than they were a year ago. Funding for basic research has diminished from 4 or 5 percent to 3 percent of the smaller pie. No one, McGroddy insists, intends to banish the highest-quality science from the elegant Yorktown Heights laboratory. But those who work there are also expected to ask what they can do for the bottom line as well as for science.

The message may be getting across. Roger H. Koch, a researcher who works on a U.S. Navy–funded contract to produce superconducting sensors, was reluctant to tell his colleagues when he began work on the project four years ago, a deferential nod to the status accorded then to pure research. "We asked ourselves, Do we want to sign up for a contract to deliver hardware to somebody?" Koch says. Those earlier attitudes have changed. "Today what we're doing is goodness," Koch comments. "There's been a real change in the perception of what's good and bad."

IBM has brought pressure to bear on some longtime researchers by making its new priorities clear. His superiors did not ask Jerry M. Woodall, a materials scientist, to pack up his belongings after 31 years at the Watson Center. "I could have stayed there and survived, but I wanted to do more than that," Woodall says. He was an IBM fellow, the corporation's equivalent of distinguished professor, which title he now holds at Purdue University. Woodall left for Purdue after the restructuring because the work he had done on creating semiconductors from gallium arsenide and other materials from the third and fifth columns of the periodic table had less value.

JOHN STARKEY Black Star

IBM ALUMNUS Jerry M. Woodall stands in front of a molecular-beam epitaxy machine that the company donated to Purdue University after the IBM veteran of 31 years took early retirement to become a professor there.

Some of the researchers at the Almaden Center had to give more thought to products and services. A group in physical sciences that used computational methods to calculate the mechanisms of basic chemical reactions moved into a "business unit" that now produces software and provides consulting.

Uncertainties about the future—and the way that IBM has cut into the perquisites of working for a company known for taking good care of its employees—can act as a powerful centrifugal tug on the researcher whom that company dearly wants to keep. Webster E. Howard was apparently one. He worked with a team that in 1966 discovered that electrons can move in two-dimensional planes parallel to the surface of a field-effect transistor, a fundamental breakthrough in condensed matter physics. "Our generation brought IBM up to be the best industrial laboratory in the world," Howard remembers.

A few years later, however, Howard decided to move into more applied areas because he felt basic research was an endeavor for the young. He organized in the early 1980s a group that developed active-matrix liquid-crystal displays, in which each pixel in the display is turned on by a single transistor. This work was incorporated into the ThinkPad laptop computer, a product that has garnered kudos for the company and serves as a concrete example of the kind of applied research the company wants to encourage. IBM has a joint venture with Toshiba for manufacturing the displays in Japan. But the research of Howard's team has given IBM as much technical depth in this critical technology as any other company outside Japan.

Howard had no intention of leaving IBM. But as the corporation's finances deteriorated, company policy became at odds with Howard's own perceptions about the value of older workers as managers of technology projects. Earlier this year IBM decided not to contribute further to the pensions of workers who had been with the company for more than 30 years. "That was a huge pay cut," Howard says. He added, "I don't think it was an intelligent policy. I think people should be judged as individuals, not by their age."

Howard says the company wanted to keep him and even offered him a big raise. (IBM had the option of denying the retirement package to employees it wanted to keep.) The increase was still not enough to make up for the gap in earnings. In June, Howard left the company to join a liquid-crystal-display development team at Bell Laboratories.

Research at IBM is by no means dead. Throughout the entire research division, there are still more than 800 Ph.D.'s working in laboratories on two coasts and another continent. But times have clearly changed for IBM research, as they did for Bell Labs and other one-time corporate jewels. What was once viewed as an investment in the future has become increasingly a current liability. Time will tell whether such accounting wisdom has laid a foundation for corporate survival. —*Gary Stix*

A Joycean Mutation

Researchers discover a new mechanism for cancer

By now molecular geneticists have worked out a fairly robust scenario for how cancer often begins. The key players are oncogenes, of which more than 100 are known, and tumor suppressor genes, or anti-oncogenes. Under normal circumstances, oncogenes and suppressor genes ensure that other genes affecting cell growth are active at the right time. When a mutation in an oncogene causes it to malfunction or when a tumor suppressor gene is lost or damaged, the genes it controls may be activated when they should not be. The result can be a cell that grows and divides but is unresponsive to signals telling it to stop.

Investigators at three institutions in the U.S. and Europe have found evidence for an entirely different type of carcinogenesis, one that accounts for a significant number of cases of colon cancer. Their work revealed that in as many as a fifth of all patients, DNA from tumors shows mutations—either additions or deletions of the base pairs that form the rungs of the DNA ladder—at numerous sites. Moreover, one group has established that a single gene is apparently responsible for the widespread genetic damage.

Manuel Perucho and his colleagues at the California Institute of Biological Research in La Jolla, Calif., first noticed in 1992 that genetic material in cells taken from some colorectal tumors had characteristic alterations in the number of base pairs at thousands of sites throughout the chromosomes. The alterations occurred at places where short sequences of bases are repeated over and over. Thus, at a particular location in a normal cell the sequence CG might be repeated 14 times. But a tumor cell might suffer 12, or perhaps 15, repetitions. Perucho speculated that patients with such tumors might have a "mutator mutation"—one that introduces errors when DNA is replicated or repaired.

Only a few months later strong support for the idea emerged from work done by Albert de la Chapelle of the University of Helsinki and Bert Vogelstein of Johns Hopkins University. About 15 percent of cases of colorectal cancer are known to be inherited. By studying families in which several members were afflicted, de la Chapelle and Vogelstein could infer that a gene in a particular region of chromosome 2—presumably a malfunctioning variant of a gene present in everyone—was causing the inherited tumors. As many as one individual in 200 carries the harmful version of the gene. For them, the chance of acquiring colon cancer by age 65 is "well over 95 percent," Vogelstein estimates. "This is as hard as nails," he declares. The same gene can predispose people to the development of other cancers as well, including cancers of the ovary, kidney and the lining of the uterus.

When de la Chapelle and Vogelstein analyzed the base sequences in DNA from tumors apparently containing the suspect gene, they found it presented alterations like those described by Perucho at many sites. Tumors from nonfamilial cases of colorectal cancer—which presumably lacked the deleterious gene—were much less likely to show such changes.

What could be the relation between a gene causing tumors and the existence of the multiple alterations in DNA? De la Chapelle and Vogelstein as well as Perucho have an idea. They speculate that the harmful gene may cause the production of a defective enzyme responsible for replicating or repairing DNA. Errors might arise for the same reason that editors have difficulty preserving the fidelity of James Joyce's wilder bouts of wordplay; the enzyme could lose its place when it is copying short repetitive sequences. The result would be DNA damage, which in turn initiates tumors. Perucho modestly calls the proposal a "plausible hypothesis." He also notes that the number of mutations in such tumors increases over time—a recent finding that supports the idea.

Similar flaws have been found in another genetic system. In September, Micheline Strand of the University of North Carolina published in *Nature* a report indicating that faulty DNA repair enzymes in yeast can cause mutations in repetitive DNA like those seen in association with inherited colorectal cancer. Moreover, other diseases besides cancer are now known to result from changes in repetitive DNA sequences. Huntington's disease, an inherited neurological disorder, and fragile X syndrome are but two examples.

Vogelstein says other inherited cancer syndromes might be caused in a comparable manner. "We are of the opinion that it is of the utmost importance to clone this gene. It is going to be very interesting and very important to find out exactly what it does," de la Chapelle says. Once that is achieved—a few months or a few years hence—tests for the presence of the gene will be relatively simple to devise. Such tests could then be used to screen relatives of patients who have colon cancer, Vogelstein states, or even the population at large. Those carrying the gene could be monitored and perhaps given preventive therapy. Because colon cancer is curable if caught early, many lives might be saved. De la Chapelle and Vogelstein are now chasing down their prey, and having sighted it, they are unlikely to give up until they have captured it.

—Tim Beardsley

Wanted: A Defense R&D Policy

Defense researchers seek to redefine their mission

For decades, the most powerful force shaping the direction of defense research in the U.S. was competition with the Soviet Union. Now, as the new world disorder emerges, the strategic landscape has completely changed. But has defense research policy? The Clinton administration has certainly uttered the right words concerning the need to shift the priorities of research spending. "In the short run, our national security depends on military might," Defense Secretary Les Aspin stated recently, "but in the long run, our national security depends on a strong economy."

Yet the vast research establishment that the U.S. constructed to counter any real or potential aggression from its archenemy stands more or less unchanged. The Department of Energy alone still spends some $3 billion a year on weapons-related research at its three major weapons laboratories, Los Alamos, Livermore and Sandia. The research and development budget of the Department of Defense now stands at nearly $40 billion a year. Defense consumes about 60 percent of the total federal budget for research and development, which is roughly equal to the total spending on research and development by the private sector. There has been no significant shift in the way funds are spent to reflect the fact that the U.S. faces not one huge potential adversary but many small ones.

Indeed, officials of the current administration, like their predecessors, insist that as U.S. forces shrink in size, advances in technology are crucial for ensuring their superiority over any potential enemy. Defense Secretary Aspin has voiced support for maintaining

SYGMA

STEALTH SHIP PROTOTYPE, designed by Lockheed to be difficult to detect with radar, exemplifies the Pentagon's continuing faith in high-technology solutions to national security problems.

R&D funds at present levels or even increasing them as the overall defense budget falls. He has suggested that this goal might be achieved through a method of weapons development he calls "rollover plus." Under the current system, explains Steven M. Kosiak of the Defense Budget Project, a watchdog group, weapons ordinarily proceed from the prototype stage directly to full-scale development. Under the rollover-plus system, Kosiak says, "instead of building just two prototypes of a new jet, say, you might build 20, so you can equip a squadron and test it operationally. Then you would have that technology on the shelf, and it would be relatively easy to go into full-scale development."

To be sure, certain research programs have been deemphasized. Continuing a trend initiated by Congress during the Bush administration, Clinton has slashed funding for studies of space-based defenses against ballistic missiles, including exotic directed-energy weapons. On the other hand, the administration is allocating more than $3 billion for ground-based defenses against ballistic missiles. Moreover, it is not yet clear whether events will permit the Clinton administration to mothball the U.S. nuclear weapons research program, as it had been expected to do. Clinton has often pledged his commitment to a nuclear test ban, but this past October, after China detonated a nuclear weapon, the president warned that the U.S. might resume its own nuclear testing program.

Defense officials have vowed to extract more value from their research spending in the future. William J. Perry, who as deputy secretary of defense is second in command at the Pentagon, elaborated on this theme in a recent interview with *Scientific American:* "Over the next decade or so, it will be more and more true that technologies that are most significant to defense are not unique to defense; that is, they are dual-use technologies."

The dual-use theme incorporates two important ideas, Perry explained. One is that the armed services, whenever possible, should use commercial technology rather than developing their own systems independently. The other idea is that in allocating research funds, the military should give priority to projects that may have commercial potential as well as defense applications.

Perry cited computer-based simulation as an example of a dual-use technology. Commercial airlines already use simulators for training pilots, and the virtual-reality interfaces, flat-panel displays and other devices that are employed in simulations have even broader applications. Perry noted that simulation provides a more cost-effective way to train not only pilots but other soldiers than field training does. "As the simulations get better, the advantages will loom larger," he points out. "There will be some cases where a computer simulation will give you more realism" than field exercises.

The lead agency in promoting dual-use technologies is the Advanced Research Projects Agency (ARPA). It has long been a major booster of advanced computing technologies, such as networking (the ARPANET was the forerunner of the Internet) and parallel processing. "It has been the premier organization for high-risk, high-payoff technologies," Perry said. "That's not new. What's new will be the emphasis on the commercial applications of technologies that are useful in defense."

The administration has authorized ARPA to dispense some $470 million in funds over the next year to private contractors for research on dual-use technologies. This past spring ARPA announced a request for proposals from contractors. Some of the proposals have been ingenious—even to the point of qualifying as special effects in *Robocop III.* One manufacturer of antisubmarine listening devices proposed that they be modified for detecting gunshots in high-crime areas.

The national weapons laboratories have initiated similar efforts to promote what officials like to call "synergy" between government and industry. On October 5, Los Alamos National Laboratory, the birthplace of the atomic bomb, announced that "in the first small business agreement of its kind" it would help a Minnesota company to improve its fabrication of printed circuit boards. Not to be outdone, the next day Lawrence Livermore National Laboratory revealed that it would lend x-ray technology developed for nuclear weapons research to a Denver company that manufactures mammography machines. "Defense Technology Converted to War against Breast Cancer" declared the Livermore press release.

But the Livermore mammography venture is worth only $3.28 million, spread over three years. The Los Alamos circuit-board initiative will cost $112,000. Even the ARPA "technology reinvestment" program shrinks into insignificance when compared with the total federal budget devoted to military research, according to John Pike, a technology analyst for the Federation of American Scientists. "So far the change is all to the right of the decimal point," he remarks.

Some national security analysts also remain skeptical that such programs will yield benefits commensurate with their costs to taxpayers. Factors that have hampered technology transfer are

the classification of research and the restrictions on the ability of federal researchers to publish or to discuss their work at conferences.

Recently, according to Steven Aftergood of the Federation of American Scientists, a defense contractor who recycles synthetic fibers was refused permission to do a literature search on that topic at the Defense Technical Information Center. On the other hand, classification and security procedures may be eased as a result of a review of the issue ordered by Clinton.

Kosta Tsipis, a national security expert at the Massachusetts Institute of Technology, thinks it is too early to expect substantial changes in spending on defense research. "The Pentagon is a very large institution and very hard to control," he notes. He agrees that the administration's policy is "a holding pattern." But he predicts that change is forthcoming, particularly as health care and other initiatives force the government to seek deep cuts elsewhere. "Next year you will be able to see what's going on," Tsipis says. —*John Horgan*

Cosmic SNUs

Closing in on the "solar neutrino problem"

For a tiny, chargeless and (maybe) massless subatomic particle, the neutrino carries a lot of scientific weight. The fusion reactions that cause the sun to shine produce neutrinos. The number of neutrinos produced is about one third less than theory predicts. Clearly, something is seriously amiss—either astronomers do not understand the internal structure of the sun, or else physicists do not understand how subatomic particles behave. Two ingenious new experiments strengthen the case for a revised physics.

The deficit first came to light around 1970, soon after Raymond Davis, Jr., now at the University of Pennsylvania, set up an underground detector, a giant tank of perchloroethylene (dry-cleaning fluid) in the Homestake gold mine in South Dakota. Subsequent observations by Kamiokande, a complementary neutrino detector located in Japan, seemed to confirm the result.

Three years ago another, quite different kind of neutrino detector—the Soviet-American Gallium Experiment, or SAGE—began operation below Mount Andyrchi in the Russian Caucasus. SAGE incorporates a 60-ton tank of liquid gallium; on rare occasions, a neutrino will hit an atom of gallium 71, transforming it into an atom of germanium 71. The number of germanium 71 atoms collected in the tank indicates the flux of solar neutrinos passing through SAGE. In 1991 a second, similar experiment—GALLEX (short for Gallium Experiment)—started operating in the Gran Sasso laboratory, deep in the side of a peak in the Apennine Mountains of Italy.

SAGE and GALLEX offer significant insight into solar physics because they are sensitive to neutrinos produced by the collision of two protons, the most fundamental energy-producing reaction in the sun. Theoretical calculations by John N. Bahcall of the Institute for Advanced Study in Princeton, N.J., indicate that the gallium detectors should pick up a flux of about 130 solar neutrino units, or SNUs, of neutrinos. In September a group of researchers affiliated with SAGE reported detecting about 70 SNUs. The 56-person GALLEX collaboration recently wrote in *Physics Letters B* that their instrument is picking up about 87 SNUs.

The numbers from SAGE and GALLEX contain a significant margin of error, so the SAGE result is regarded as totally consistent with GALLEX, according to Michael L. Cherry of Louisiana State University. Models of the sun also contain some uncertainties. But are the errors so large that they may be able to explain away the solar neutrino problem? Douglas R. O. Morrison of CERN, who often places himself at odds with established theorists, thinks they are. "I see no compelling evidence" of a solar neutrino problem, he declares.

Bahcall and Cherry take a rather different view. They note that the combined evidence of four neutrino detectors, all of which find a peculiarly low number of solar neutrinos, persuasively argues that the solar neutrino problem is real. Bahcall and Hans A. Bethe of Cornell University have run 1,000 computer simulations of the sun's internal physics; none yielded anything close to the observed neutrino flux. Even if the neutrino counts contain some systematic error, Bahcall adds, the relative numbers detected at various energies contradict theoretical expectations. Richard L. Hahn of Brookhaven National Laboratory, who participates in GALLEX, agrees that "in the standard solar model, it's pretty tough to match the solar neutrino experiments."

So, where have all the solar neutrinos gone? In a theory originated by Lincoln Wolfenstein of Carnegie Mellon University and elaborated by Russian physicists Stanislaw P. Mikheyev and Aleksei Y. Smirnov, neutrinos "oscillate" between different types. According to their theory, known as the MSW effect, the electron neutrino, which shows up in existing detectors, could transform into other forms of electrons that the detectors cannot collect.

One of the corollaries of the MSW effect is that the neutrino, long thought to be a massless particle, must possess a tiny mass. For years, some cosmologists have wondered if mass-bearing neutrinos could make up part or all of the cosmic "dark matter"—an unseen component of the universe whose gravity may strongly influence the evolution and dynamics of galaxies. Should the solar neutrino results stand up, it would yield an additional bonus: support for the version of the Grand Unified Theory (which attempts to unite all the forces of nature except gravity) on which the MSW conjecture is based.

"It is still a bit of a crapshoot at this point," Hahn says, "but at the conferences, people are talking more and more about oscillations." Several upcoming neutrino detectors may finally sort out this mess. The most important may be the Sudbury Neutrino Observatory in Canada, which will be able to detect all forms of neutrinos and so should finally clarify whether the MSW theory is correct. —*Corey S. Powell*

CHIOLINI

GRAN SASSO LABORATORY houses GALLEX and other ongoing neutrino-detection experiments. The underground location reduces false signals from stray radiation.

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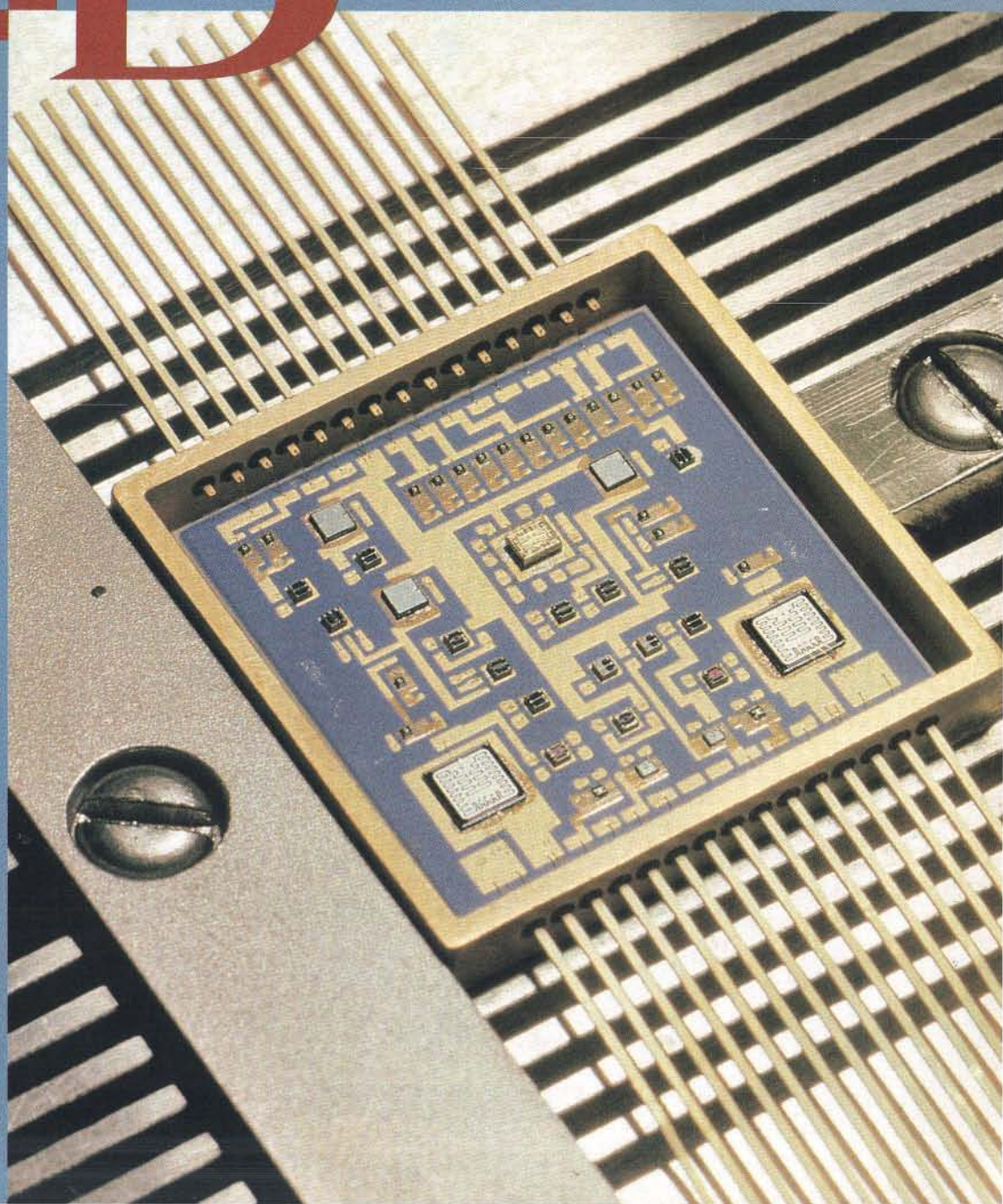
R+D Report 1993



TECHNOLOGY FOR TODAY AND TOMORROW

By Toshio Nakatsubo,
Senior Managing Director & Executive Director,
Corporate Research, Olympus Optical Co., Ltd.

Toshio Nakatsubo

Next year, the Olympus Optical Co. will celebrate its 75th anniversary as a leader in electronic technology and sophisticated optical research. In commemoration of this important landmark, we have selected the motto "Fresh & Excellent" to symbolize both our past achievements and long term goals. Now, as the 21st Century beckons, we are committed to the aspirations and ideals that have helped us make unique contributions to the Japanese and world economies. Likewise, our priorities remain the same: to create a workplace where our employees can determine their own goals while continuing to offer quality and complete customer satisfaction.

Combining Industry With Service

Olympus Optical places an emphasis on three specific areas of business — image, information and telecommunications; medicare and biotechnology; and semiconductor-related products. We have structured our R&D strategy to best reflect and optimize this emphasis, and in particular, we are striving to switch from conventional secondary industry based on manufacturing to the "2.5th" industry, which also contains a service dimension. For instance, Olympus not only develops "stand-alone" products such as cameras, but also promotes the creation of systems and software which use these products as a foundation and add to their performance.

Seven key areas of technology — optics, information processing, electronics, functional materials, medical-related technology, precision, and biotechnology — will be essential in promoting and complementing our business areas. We have placed a special importance on image input technology, digital data compression and storage technology, and electronic transmission and output technology — all of which are used in electronic cameras. Of these, in the field of displays, we have already begun marketing spectacle-type, head-mounted displays, which show three-dimensional images.

In other areas, over the medium- and long-term, we are working on the development of endoscopes and other medical products that utilize new advancements in microtechnology. Endoscopes are already used routinely in many medical operations, but the next few years promise exciting advances in this field. The endoscope of the future will itself become a micro-robot, moving toward diseased parts of the body and producing the necessary tools for assistance. We also hope to consolidate element technologies such as system control and provision of energy.

> WE HAVE SELECTED THE MOTTO "FRESH & EXCELLENT" TO SYMBOLIZE OUR PAST ACHIEVEMENTS AND LONG TERM GOALS.

Global and Environmental Concerns

Our company became globalized at an early stage. We have a number of manufacturing and sales units overseas and have strong ties with U.S. companies in R&D and developing new businesses. Foremost among our efforts are a new, two-dimensional bar code system created through a joint venture with Symbol Technologies Inc. and new surgical tools to be used with endoscopes that have been developed in cooperation with Ethicon Emdo Surgery Inc., a division of Johnson & Johnson. We are also collaborating with U.S. companies in developing electron-beam printers which make use of ions and optical cards and can be used to store individual medical records. Furthermore, our Biomedical Research Center unit in New York symbolizes the spirit of cooperation that characterizes our efforts in the field of scientific research.

Global environmental issues have long been a concern for Olympus as well. In 1982, we joined the World Wildlife Foundation, and our corporation's own Ecological Environmental Protection Department helps strengthen our environmental awareness. In the coming years, we will work to develop systems which are friendly to the earth, safe for the human body, and recyclable. We have already developed cleansing equipment and agents for lenses and other optical items that do not use chlorofluorocarbons, and in March, 1993, we prohibited all uses of CFCs in our company — a mandate that applies to metal parts and semiconductor substrates as well. In the future, we hope to continue to contribute to the global environment as part of our corporate activity.

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There's very little you can't do with the Olympus Zoom Lens Reflex series. The all-in-one cameras that won't limit your creative ability.

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Finally, with the IS-2000 you have a built-in 35mm – 135mm zoom lens, and with the IS-3000 it's a 35mm – 180mm zoom. All made with our exclusive ED (Extraordinary Dispersion) glass that lets you take telephoto and macro close-ups that are both clear and sharp.

The Olympus IS-2000 and IS-3000. There's no limit to what you can do.

IS-2000

IS-3000

In North, South and Central America the IS-2000 and IS-3000 are sold as the IS-2, and IS-3 respectively.

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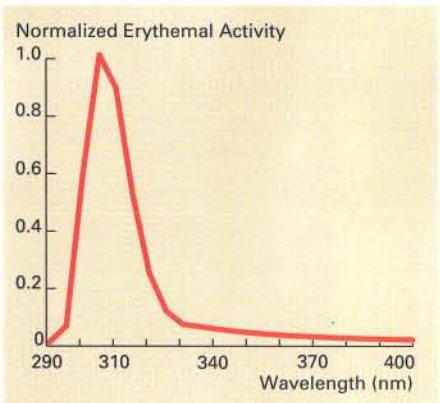
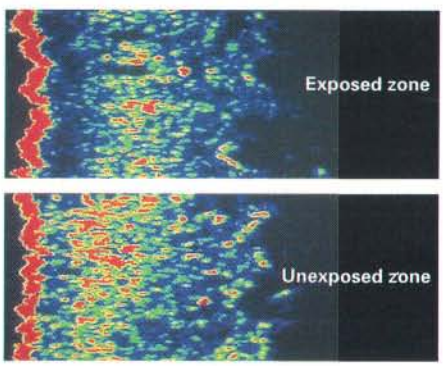
L'ORÉAL

MEXORYL SX®: a friend for the sun



The effects of solar radiation on the skin. The curve shows the appearance of sunburn (erythema), indicating a maximum for UVB rays at 305 nm, and extending into the shortwave scale of the UVA range.



Exposure to sunlight induces significant alteration in the dermis, resulting in photoaging of the skin. UV damage includes lesions of the basal-cell membrane which separate the epidermis and the dermis. This can be seen with the aid of ultra-sonic imaging techniques.

L'Oréal's emphasis on research and development and its pioneering work in skin care have made a major contribution to the understanding and protection of human skin. A key area of L'Oréal research is the development of suncare products that allow the benefits of sunbathing while shielding human skin from the harmful effects of prolonged exposure to ultraviolet (UV) radiation. One of the most recent fruits of L'Oréal research in this area is the new UVA sun filter, MEXORYL SX.

The ultraviolet rays of the sun, UVA and UVB, forming two adjacent ranges of the electromagnetic spectrum, differ in intensity according to their wavelengths.

The earliest sun lotions, introduced in 1930, blocked out UVB radiation only, leaving UVA radiation unfiltered because it was not believed to be harmful. It is now generally accepted that overexposure to sunlight damages the skin, causing erythema or sunburn, degeneration of elastic tissue, actinic aging, and various forms of skin cancer. The effects of this exposure are directly related to the wavelength and dosage level of ultraviolet radiation and involve both UVA and UVB radiation.

The more harmful UVB rays are of shorter wavelength (290/320 nanometers) and are responsible for the most severe long-term consequences of solar radiation, including an increased susceptibility to skin cancer. Although the longer UVA rays (320/400 nm) are lower in energy, they are more abundant and can also cause damage to the skin, particularly the rays at the shorter end of the UVA range (320/340 nm). Prolonged exposure to UVA radiation, which penetrates glass and human skin, causes premature skin aging, photodermatosis and can also play a role in photocarcinogenesis. Although UVA radiation may cause less sunburn than UVB, there is evidence that the harmful effects of the sun require skin to be protected against both UVA and UVB radiation.

When L'Oréal began research into UVA filters in the 1980's, it found that although there were many efficient UVB filters available, UVA filters were inadequate. They had formulation problems because of poor solubility or poor efficiency and they were also unstable when exposed to sunlight.

A new photostable UVA filter with the same practical characteristics as the UVB filter had to be found. The new filter would have to be highly protective and absorbent in the range of 320/400 nm, stable in sunlight and heat, resistant to perspiration, easy to formulate (soluble and compatible with cosmetic ingredients), well tolerated (neither toxic, phototoxic nor an irritant), odorless, non-staining, and affordable.

The stability of a sunscreen agent is crucial. Energy absorbed by the molecule when exposed to UV light triggers photochemical excitation of that molecule. Reversal of the molecule to its original condition results in conversion of UV radiation into thermal energy, which is harmless. In this way, when the energy of UV radiation is absorbed by a filtering molecule on the surface of the skin, it does not reach the deeper levels where it could cause harm. When the photostability of the filter is poor or absent, this process results in degradation and loss of protective efficiency over time.

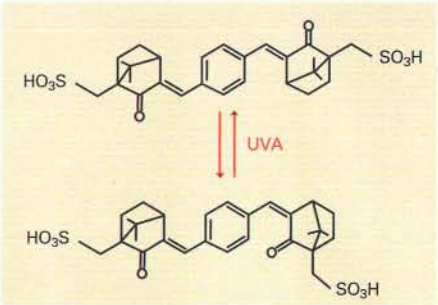
Photostability could be achieved easily for UVB filters, but this was not the case for UVA filters. Earlier L'Oréal studies had shown benzylidene camphor to be one of the most suitable UVB filters, mainly because of its high level of photostability. L'Oréal chemists therefore decided to adapt this UVB filter to UVA radiation. They created several dozen molecules by grafting different chemical substituents onto the basic structure of benzylidene camphor. At the same time, a battery of photochemical tests was developed to assess the effects of light-exposure on the synthesized molecules.

Benzylidene camphor derivatives were found to have excellent photostability due to their capacity for reversible isomerization in solution as well as in emulsions applied to human skin.

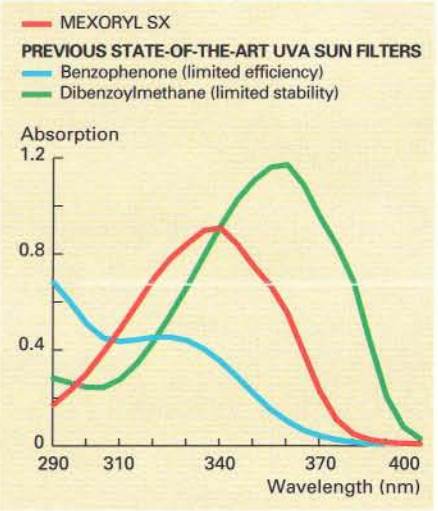
However, when tested for compliance with the specifications for an ideal UVA filter, most of the new molecules were rejected. Some, although stable in sunlight, were colored and would stain clothing; others were eliminated because of poor solubility; others again were not considered safe enough from a toxicological point of view. The molecule finally selected to be adapted for protection against UVA radiation was MEXORYL SX.

MEXORYL SX has all the properties that a good sunscreen agent should have. It has a maximum absorption of 345 nm, corresponding to the limit between short and long UVA rays. Its high photostability has been demonstrated *in vitro* and in tests on humans. Moreover, although most UV filters are found only in the oil phase of an emulsion, MEXORYL SX has the added advantage of being hydrosoluble and thus increases efficiency when combined with lipophilic filters.

With the introduction of MEXORYL SX, L'Oréal has made possible the first effective, photostable UVA filter. This highly promising molecule, which is the culmination of many years of L'Oréal research, represents a major advance in UVA photoprotection and has opened the way to a new generation of suncare products.



MEXORYL SX isomerizes on exposure to UVA wavelengths. As this reaction is reversible, MEXORYL SX offers enduring protection.



The characteristics of the MEXORYL SX absorption spectrum make it an ideal UVA filter.

HIGHLIGHTS OF L'ORÉAL'S SUN PROTECTION ACTIVITY

1936
L'Oréal launches the first range of suncare products in France

1968
First L'Oréal patent using benzylidene camphor

1972
First L'Oréal patent on a new benzylidene camphor family for UVB protection

1981
Start of the UVA protection project

1982
MEXORYL SX is patented

1991
MEXORYL SX is approved by the EEC

1993
Marketing in Europe of the first range of suncare products using MEXORYL SX

Overall, more than 40 patents have been filed in the sun protection sector.

SCIENTIFIC AMERICAN

The Fertility Decline in Developing Countries

Family size is decreasing in many Third World countries. The reasons provide the key to slowing population growth

by Bryant Robey, Shea O. Rutstein and Leo Morris

The developing world is undergoing a reproductive revolution. Throughout the Third World, women differing vastly in culture, politics, and social and economic status have started to desire smaller families. Birth rates have declined by one third since the mid-1960s: women formerly had six children on average, but today they have four.

Contrary to the expectations of many observers, developing nations are not experiencing the classical demographic transition that took place in many industrialized countries over the past century. In the U.S. and the U.K., for instance, declining birth rates came only after economic growth had brought improvements in health care and education. The transition took many decades.

In contrast, recent evidence suggests that birth rates in the developing world have fallen even in the absence of improved living conditions. The decrease has also proceeded with remarkable speed. Developing countries appear to have benefited from the growing influence and scope of family-planning programs, from new contraceptive technologies and from the educational power of mass media.

Such findings have extraordinary implications for future efforts to slow population growth. For despite the observed decrease in birth rates, the world's population continues to burgeon: the number of people is expected to double to 10 billion by 2050. It has been estimated that 97 percent of this increase will occur in the developing world, where more than one third of the population is younger than 15 years—that is, these individuals are just entering their reproductive years.

By examining the results of recent demographic and family-planning surveys, we have been able to study the direct and indirect causes of falling birth rates in developing countries and to clarify how they differ from the demographic transition of the West. Using these insights, we can pinpoint how most effectively to encourage this unexpected and welcome revolution.

The most recent data about fertility in developing countries are drawn from 44 surveys of more than 300,000 women conducted over the past eight years. These surveys were of two types: the Demographic and Health Surveys, carried out by Macro International, Inc., and the Family Planning Surveys, coordinated by the U.S. Centers for Disease Control. Both were funded in large part by the U.S. Agency for International Development and collected nationally representative, comparable information. The surveys were undertaken in 18 countries in sub-Saharan Africa, 16 in Latin America and the Caribbean, six in the Near East and North Africa, and four in Asia. Independent national surveys provide some data for six additional Asian countries, including China, India and Bangladesh.

These inquiries continue an international effort that began 20 years ago. Before the 1972 World Fertility Survey, no attempt was made to collect comparable and comprehensive data on fertility and family planning from developing nations. Now more than 30 countries have recorded such material, both in the World Fertility Survey, which ended in 1984, and in the current round of surveys that began in 1985. Using these records, demographers can chart trends in fertility and family planning over two decades. Together, these programs represent one of the most comprehensive

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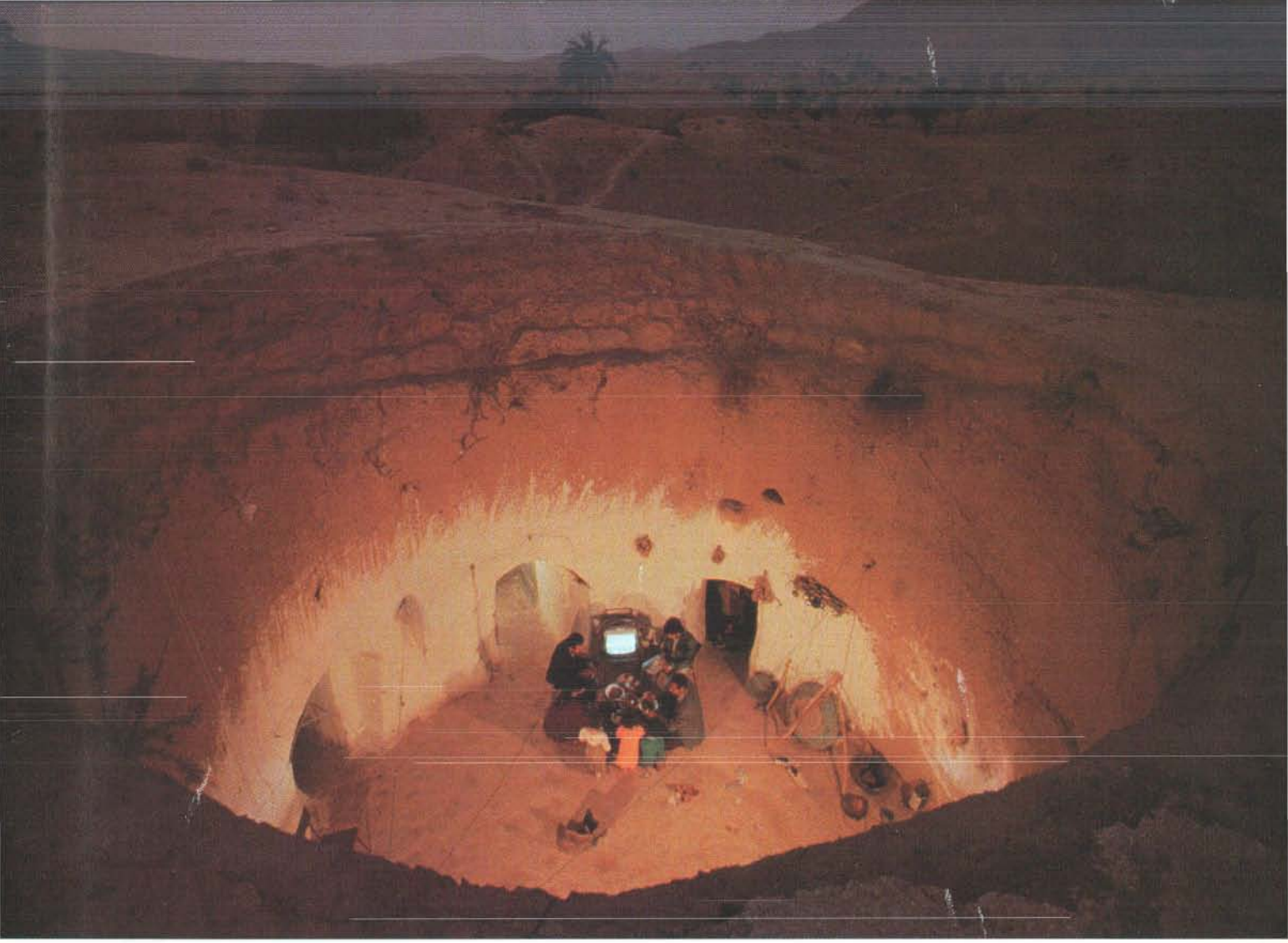


MASS MEDIA penetrate into the cave of even the most remote family in Tunisia. Television and radio can carry popular shows that encourage family planning. Consequently, they have contributed to declining fertility rates in some developing countries. In Tunisia, the birth rate fell from six to 4.3 children per woman between 1978 and 1988.

research efforts in the social sciences.

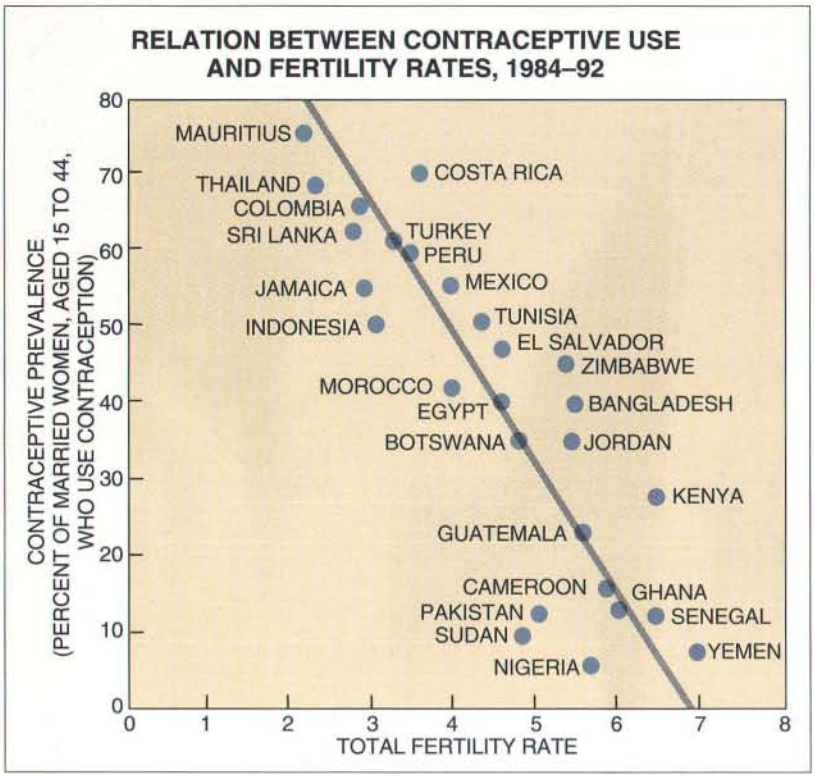
These large-scale data bases make available unique information about the reproductive attitudes and behavior of women in the developing world. In each country surveyed, women of childbearing age were randomly selected and asked more than 200 questions about their reproductive history, their attitudes and preferences about childbearing as well as their knowledge and use of contraception. They were even asked about sensitive topics such as the frequency of their sexual relations. Statistics about age, marital status, education and household possessions, such as radios and televisions, were also gathered—both to measure social and economic status and to observe any impact technology may have on fertility rates and the use of contraception.

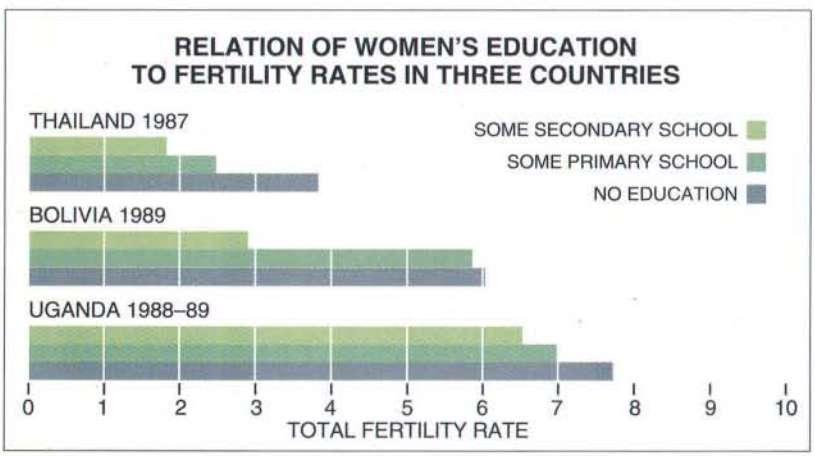
To compare the fertility levels of various countries, of groups of women or of time periods, demographers calculate a figure called the total fertility rate. This statistic is based on data provided by women between the ages of 15 and 44 about the number of times they have given birth. Calculations are made of the average number of births per year in each five-year age group, and these are added together to yield the total fertility rate. The total fertility rate represents the number of children a typical woman would have during her reproductive lifetime if she were to follow current fertility rates.

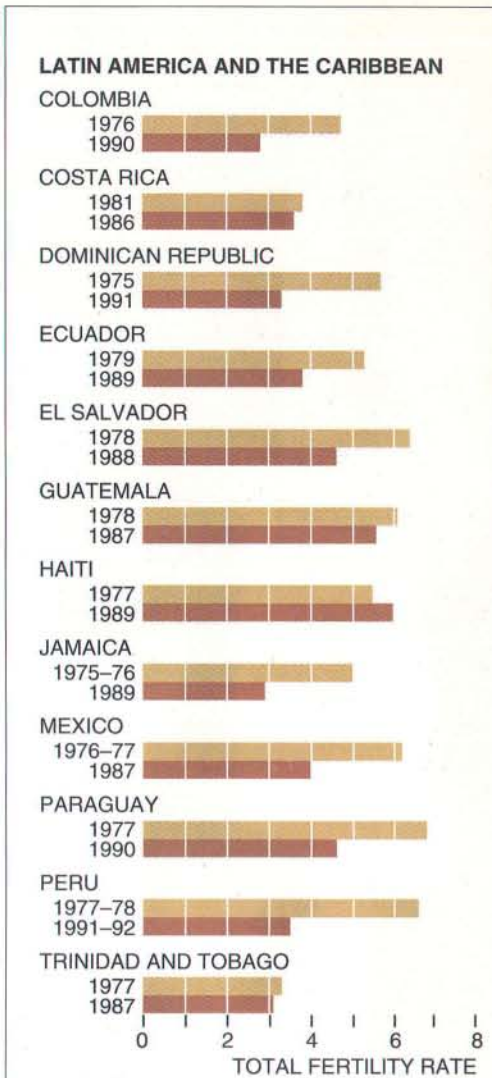
Those numbers show that fertility rates have declined dramatically since the 1970s. In Thailand, for instance, fertility plummeted 50 percent in 12 years: from 4.6 children per woman in 1975 to 2.3 children in 1987. In Colombia, the fertility rate fell from an average of 4.7 children per woman in 1976 to 2.8 children in 1990. In Indonesia, fertility declined 46 percent between 1971 and 1991; in Morocco, it dropped 31 percent between 1980 and 1992; in Turkey, fertility decreased 21 percent between 1978 and 1988. In eight Latin American and Caribbean countries, women today are having an average of one fewer child than did women 20 years ago.

Of course, many factors, direct and indirect, have brought about these changes. In the 1950s demographers Kingsley Davis and Judith Blake—and, more recently, John Bongaarts of the Population Council in New York City—described the four major direct influences on fertility. They are the use of effective contraception, the age at which women first marry, the length of time after childbirth that a woman cannot conceive (because of breast-feeding or sexual abstinence) and the use of abortion. Unfortunately, information about the role of abortion in developing countries remains largely obscure. Abortions are known to limit fertility substantially, but researchers have difficulty collecting accurate information about abortions from women, particu-

Fertility Rates and Their Relation to Education







The total fertility rate is the average number of children a woman bears in her lifetime.

larly when and where they are illegal. According to Bongaarts, education, occupation, wealth, location, religious belief and social status are indirect determinants of fertility. Because they are indirect, their effect on fertility is less easily interpreted.

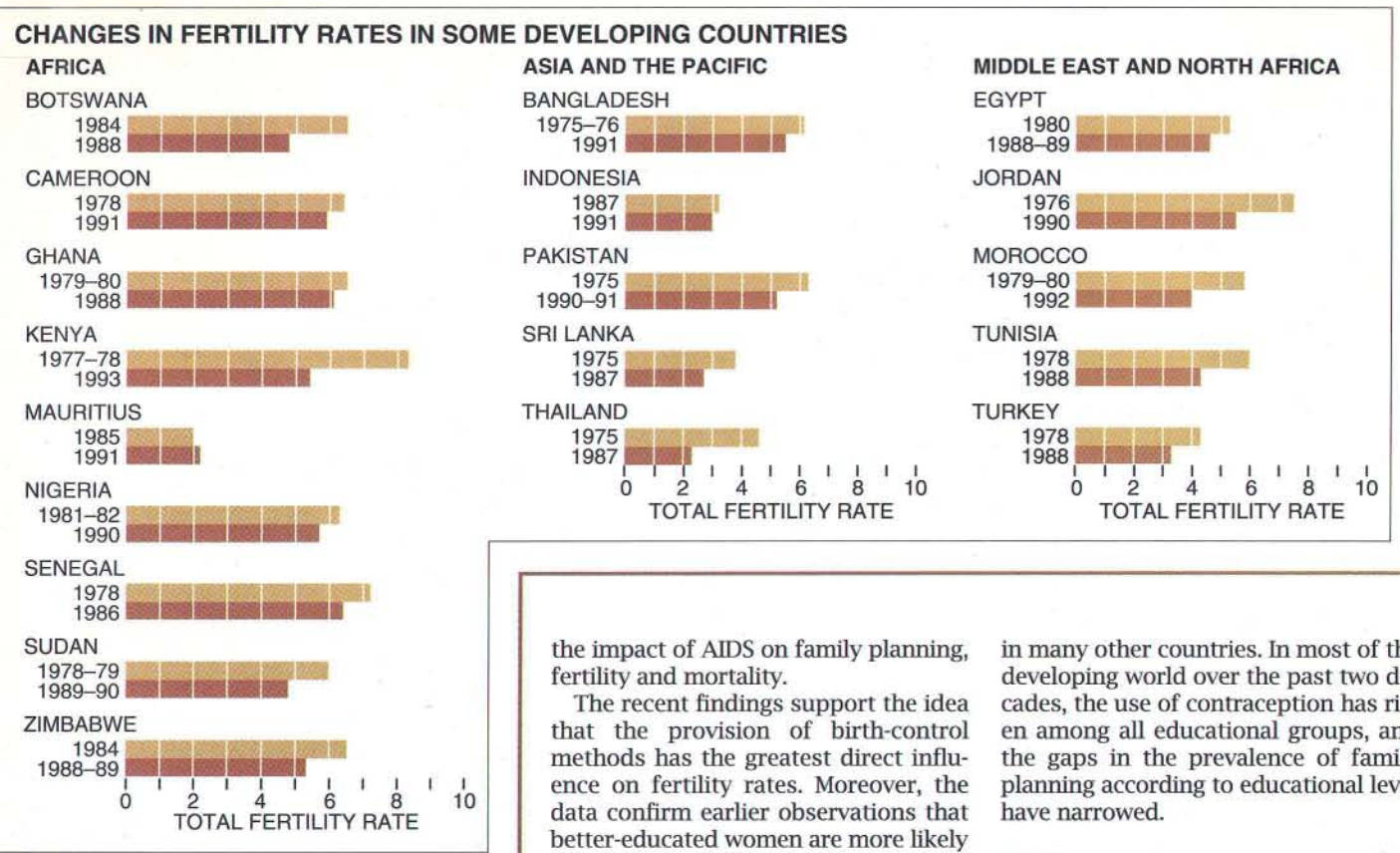
Of the direct influences, the most powerful is family planning. A country's contraceptive prevalence rate—the percentage of married women of reproductive age who use any method of contraception—largely determines its total fertility rate. Indeed, the data reveal that differences in contraceptive prevalence explain about 90 percent of the variation in fertility rates. In general, if contraceptive use increases by 15 percentage points, women bear, on average, one fewer child. The survey results indicate that fertility levels have dropped most sharply where family planning has increased most dramatically.

Excluding China, 38 percent of married women in their childbearing years in developing countries now practice family planning—a total of some 375 million women. (If China is included, the figure rises to 51 percent.) In contrast, more than 70 percent of married couples in most industrialized countries use contraception. And in Japan and some western European countries, the total fertility rate is approaching, or is below, the replacement level of 2.1 children per couple—the rate at which the population eventually stops growing.

As access to newer forms of contraception has spread in the Third World, couples have become less likely to depend on traditional methods such as periodic abstinence (the rhythm method) and withdrawal. Among the countries surveyed, traditional methods are predominant only in four African countries in which there is very little use of any contraception and in which fertility is high: Burundi, Cameroon, Ghana and Togo. In one Latin American country, Bolivia, 17 percent of the married women rely on the rhythm method—a number higher than that of women practicing modern methods.

Today 80 percent of the married

and Birth Control in Some Developing Countries



women in the Third World who practice contraception employ recently developed methods. According to the questionnaires, voluntary female sterilization is the most common method of family planning. Sterilization is prevalent throughout Latin America and the Caribbean, where it is the leading method of contraception in nine of the 16 countries surveyed. Voluntary female sterilization is also the most widely used method in India and is a close second to the intrauterine device (IUD) in China. In Latin America, many women choose sterilization because they reach their desired family size soon after marriage: couples have an average of three or four children and typically do not space the births very widely apart. Sterilization is uncommon in the countries that were studied in Africa and the Middle East.

Despite the AIDS epidemic, only about 4 percent of married couples of reproductive age in developing countries use condoms for family planning. Although there are only limited data, it appears that condom use may be rising in response to AIDS, particularly among unmarried people. Future surveys are planned to gather new information on the impact of AIDS on family planning, fertility and mortality.

The recent findings support the idea that the provision of birth-control methods has the greatest direct influence on fertility rates. Moreover, the data confirm earlier observations that better-educated women are more likely to practice some form of contraception than are women with little or no education. The results show that women in urban areas are more likely to use contraception than are women living in rural parts of the country. Women in cities tend to be better informed than their rural counterparts and are more exposed to contemporary attitudes, including a desire for smaller families. Raising children can also be more expensive in cities, conditions are crowded and urban couples have less need for child labor than those in agricultural areas. Perhaps most important, family-planning services and supplies are more readily available in cities.

Yet the surveys also demonstrate that having an education or living in a city is not a prerequisite for using contraception. In some countries in which methods of birth control have become more widely available and interest in smaller families has spread, fertility has declined substantially among rural and less educated women. In Colombia most of the country's fertility decline during the 1980s was the result of increasing use of family-planning services by less educated women. In Indonesia, where the government family-planning program has tried to reach every couple, fertility has fallen among all members of society more equally than in many other countries. In most of the developing world over the past two decades, the use of contraception has risen among all educational groups, and the gaps in the prevalence of family planning according to educational level have narrowed.

The changes that can be seen in the fertility rates of three sub-Saharan countries strikingly illustrate this new trend. Before the data became known, many experts doubted that sub-Saharan Africa would join the reproductive revolution anytime soon. Traditional beliefs and kinship systems supported high fertility [see "High Fertility in Sub-Saharan Africa," by John C. Caldwell and Pat Caldwell; SCIENTIFIC AMERICAN, May 1990]. Nevertheless, since the 1970s, fertility declined 26 percent in Botswana, 35 percent in Kenya and 18 percent in Zimbabwe. These countries differ from most of sub-Saharan Africa in the demand for and the availability of family planning.

Despite these differences, Botswana, Kenya and Zimbabwe could represent the vanguard rather than the exception. In Kenya, for example, the culture favors large families. Early attempts to encourage family planning made little progress. But as rapid population growth began to put pressure on agricultural land and to swell the cities, the appeal of big families diminished. Better education and rising status of women also promoted a new view of family size. At the same time, strong commitments by the Kenyan government and donor organizations have enabled the country to meet a large part of the de-

mand for contraceptives. Between 1984 and 1989 contraceptive use rose 59 percent, and the number of children desired declined 24 percent. Fertility fell 16 percent.

Traditional attitudes and women's status are changing elsewhere in sub-Saharan Africa. Even in countries where few couples use contraception, research shows that educated women do not think that large families endow them with social and economic status or that fate determines family size. Women are marrying later: although sub-Saharan women generally wed earlier than do women in other places, the age at first marriage has risen in virtually every surveyed country during the past 20 years. Cultural patterns in many African countries remain substantially different from those in Asia or Latin America, and polygyny is still widely practiced, but these patterns are changing.

Contraception is becoming more acceptable in sub-Saharan Africa as well. In particular, educated and urban women are starting to practice family planning. In Niger, 16 percent of the women living in cities seek family planning as compared with 3 percent of rural women. In Nigeria, the most populous country in Africa, with over 90 million people, national surveys show contraceptive prevalence rose from 6 percent in 1990 to more than 11 percent in 1992.

Although most African women tell survey-takers that they want large families, they frequently report interest in spacing births. In the countries of sub-Saharan Africa studied, between one fourth and one third of women want to wait at least two years between births. This desire is a sign that if African governments did more to promote and provide effective contraception, more women would be likely to use it.

Sweeping changes are occurring outside sub-Saharan Africa. At least half of the women in 16 of 22 countries said that they do not want more children. The number of married women who feel this way has risen nearly everywhere. This figure has proved to be a good short-term predictor of fertility rates. Based on survey data, Charles Westoff of Princeton University projected in 1991 that fertility rates will decline further by 13 percent in Latin America and by 10 percent in Africa by 1996.

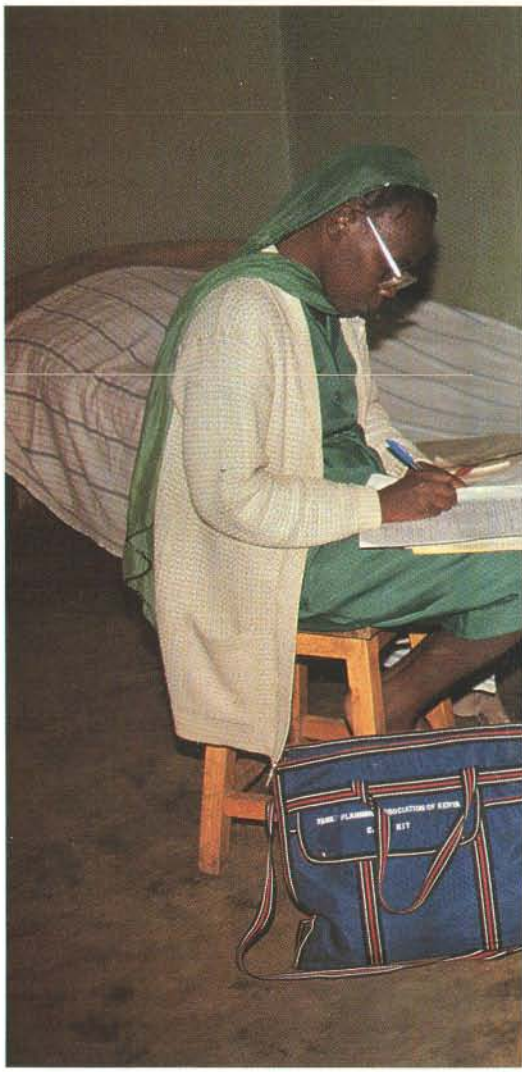
Decreases in fertility rates seen in these countries are fundamentally different from those that occurred in the industrialized countries several generations ago. To explain Europe's broad fertility decline in the century or so after the Industrial Revolution, social scientists developed the notion of a demographic transition. Death rates fell in Europe in the 1800s as living conditions improved and as medical science advanced. Population grew rapidly as a result, spurring migration overseas. Eventually, in the 1900s, birth rates fell, slowing population growth.

Demographic transition theory reflects this pattern. It holds that societies are initially characterized by high fertility and high mortality: the population does not grow. This phase is followed by an intermediate stage in which modernization begins and mortality is reduced but fertility remains high. This period is one of rapid population growth; only later does fertility decline. The last era, one of stable population growth, low mortality and low fertility, describes most of the developed world.

The recent decline in fertility rates among developing countries does not fit this theoretical framework well with respect to timing or to circumstance. Fertility rates in developing countries have fallen much more rapidly than they did during the European demographic transition. Even in poor countries that were relatively untouched by development, new attitudes have taken root, and more couples are having smaller families. In fact, fertility declined as many developing economies stagnated or lost ground in the 1980s.

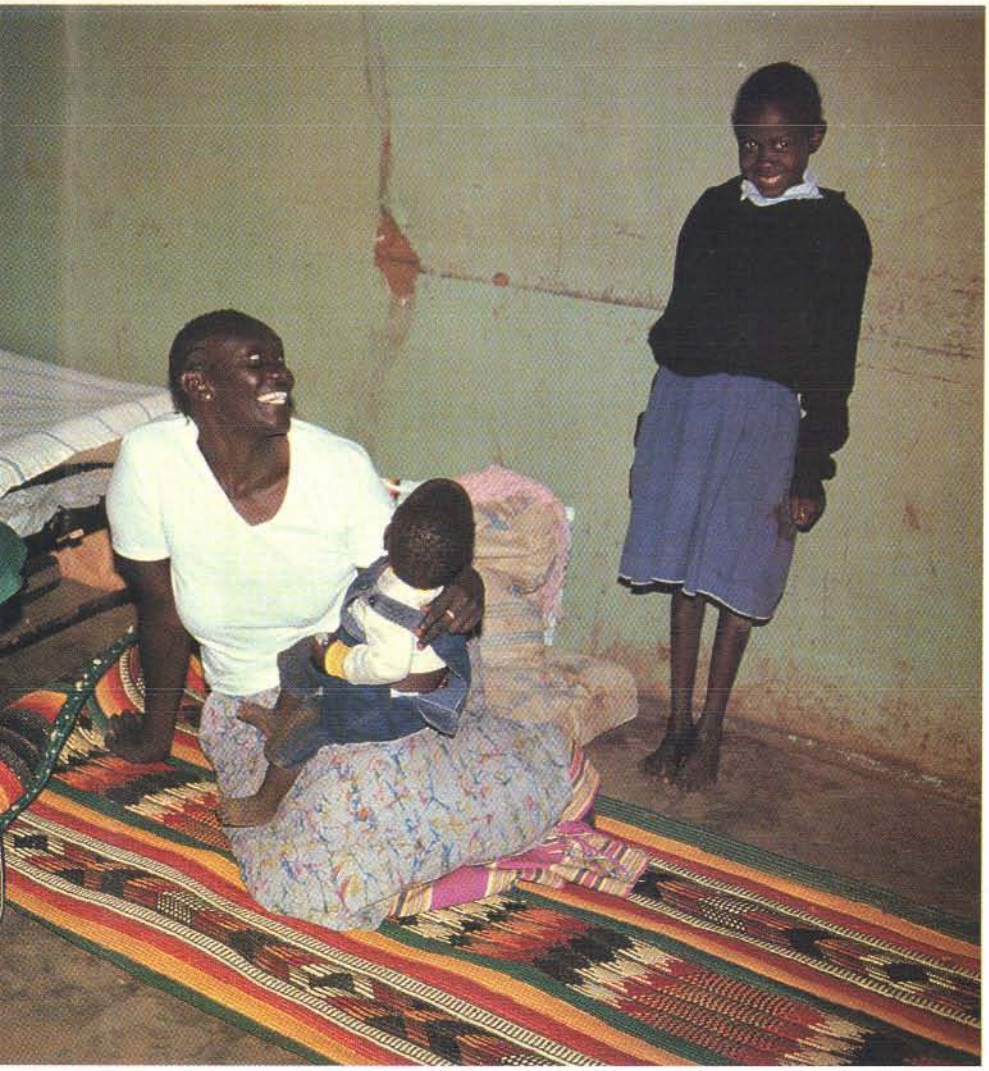
The findings dispute the notion that "development is the best contraceptive," a phrase that originated at the 1974 World Population Conference in Bucharest. This view held that fertility would not drop until developing economies improved. Bangladesh is a perfect example of how this concept has been disproved. It is one of the world's poorest and most traditional agrarian countries. Infant mortality is high, women have low social status and most families depend on children for economic security. Nevertheless, fertility rates there declined 21 percent between 1970 and 1991: from seven to 5.5 children per woman. During this period, the use of contraception among married women of reproductive age rose from 3 to 40 percent.

The differences between fertility declines in developing countries today and those seen in Europe may best be explained by differences in the approaches to family planning. During the West's demographic transition, modern contraceptive methods were not yet invented, and the concept of family planning was not quickly accepted. Those who spoke out in favor of contraception were often castigated. For example, when Margaret Sanger, a pioneer of the birth-control movement, opened a clinic in Brooklyn in 1916, she was arrested for creating a public nuisance. Information about contraception diffused slowly because educational levels were low and mass communication was limited.



The availability of effective contraception gives contemporary developing countries a major advantage over the European societies that underwent fertility declines earlier. Before modern, effective contraceptive methods existed, most Europeans used abstinence, withdrawal and abortion to control their family size. In several countries, primarily in eastern Europe, couples still rely on such practices because newer forms of birth control are in short supply.

As contraceptive methods such as the pill, IUDs, injectables and sterilization have been developed, governments and donor agencies have helped developing countries establish family-planning programs and provide contraception. These services have sought clients and have removed or lowered many of the economic barriers to health care and to the availability of contraception.



FAMILY-PLANNING CLINICS, such as this one in Kenya, have made birth control and medical services more readily available. According to 1993 data, 33 percent of married women use contraception—up from 27 percent in 1989.

Widespread communication and the influence of mass media in developing countries have accelerated the diffusion of novel ideas about family planning in both urban and rural environments. Unlike past generations, millions of people now have direct and instant access to the rest of the world through radio and television. Analyses of the surveys in Ghana and Kenya show that mass-media campaigns have shaped women's family-planning decisions. Research by Westoff and demographer Germán Rodriguez, also at Princeton, found that Kenyan women who listened to or watched family-planning messages on radio or television were more likely than others to want smaller families and to use family planning. Similar surveys in Nigeria, the Gambia and Zimbabwe have found the same trends. Phyllis T. Piotrow and her colleagues at the Johns Hopkins School of Hygiene and Public Health found that three Nigerian popular entertainment shows containing messages about family planning more than doubled—and in one city quadrupled—the number of clients at family-planning clinics. Many developing countries are adopting such approaches to gain acceptance for contraception.

Greater availability and promotion of modern family-planning methods have enabled couples to control their family size more effectively than they could only a decade or two ago. These conditions set the stage for the rapid drop in fertility rates of the past two decades. In most developing countries the spark that changed the long-held attitudes toward having large families came not from modernization but from the sharp economic contractions of the late 1970s and early 1980s. For the first time, many families found that their standard of living fell. In response, couples decided to limit their family size or to postpone the next birth. This trend is unlikely to reverse.

Thus, in Thailand, Indonesia, Colombia, Kenya and many other Third World nations, the pervasive adoption of family-planning methods and dissemination of new ideas have caused fertility to decline so rapidly that it may be more accurate to speak of a reproductive revolution rather than a demographic transition.

Our review of the data suggests that although development and social change create conditions that encourage smaller family size, contraceptives are the best contraceptive. Research by W. Parker Mauldin and John Ross of the Population Council indicates that—independently of the effect of social and economic changes—family-planning programs played a significant role in reducing fertility in developing countries between 1975 and 1990. One of us (Rutstein) has shown that changes in contraceptive use and in fertility depend as much on the strength of a country's family-planning effort as on its economic development.

In addition, researchers increasingly emphasize the diffusion of different attitudes and values as a powerful force behind fertility decline. Such "ideational change," in the words of John Cleland of the London School of Hygiene and Tropical Medicine and Christopher Wilson of the London School of Economics, may explain the 50 percent drop in fertility in Thailand between the 1970s and the 1980s. Most Thais share a common culture that is open to change, and many of the rural areas are linked to the national economy. Shifting ideas about birth control and greater opportunities to obtain education, employment and consumer goods swiftly reached regions outside the cities, helping to generate a demand for family planning. Thailand's energetic national family-planning program encouraged and met the rising demand.

Despite the fertility declines, it is unclear when the developing world in general will reach the same level of contraceptive practice as is found in a few Third World countries and in the developed world. Although couples nowadays have, on average, fewer children than did couples before them, the number of women of reproductive age continues to rise. In the most populous countries, such as India, fertility far exceeds replacement level. The world's population is still growing rapidly. For fertility to fall to levels that will slow population growth rates substantially, effective contraception must be used by

Marriage, Children and Family Planning in Selected Countries

MARRIAGE AGE is rising in many Asian countries—including Singapore, where this couple were wed—and throughout the developing world. Older age at marriage can foster lower fertility. Teenage marriages, however, remain common in some places.

an ever larger share of the population.

The pace at which fertility will keep decreasing is likely to depend on three interrelated factors: how fast societies develop; how quickly new norms concerning small families and the use of family planning are accepted; and, perhaps most important, how well public programs and private suppliers can meet the need for contraception. The demand for family planning already far surpasses its supply. In the countries surveyed, between 20 and 30 percent of married women are not using contraception even though they want to avoid pregnancy. These women are said to have an unmet need, or unsatisfied demand, for family planning.

Estimates vary, but demographers agree that a substantial unsatisfied demand for family planning exists in many countries. More than 120 million married women of reproductive age are not practicing family planning even though they report in the surveys that they wish to avoid pregnancy, according to Richard Blackburn of the Johns Hopkins Population Information Program. This figure is based on an extrapolation of data from 50 developing countries to all other developing countries, weighted by population size. The number amounts to more than one woman in every five in the developing world, not including China. (In China, there is presumed to be no unmet need because of the wide availability of contraception and the government's policy of one-child families.)

In every country outside sub-Saharan Africa—except for Haiti and Pakistan—most married women of reproductive age already use family planning or desire family planning. In Asian and Latin American countries, most of the demand for family planning is already being met. In 14 African countries surveyed, however, less than half the potential need is satisfied. In fact, in most sub-Saharan countries less than one third of the potential demand for family planning is satisfied, and less than one fifth is met in Liberia, Mali and Uganda. The unsatisfied demand is greatest in rural areas, where contraception remains for the most part unavailable. Such statistics offer clear evidence that the supply of birth-control methods is still far from ideal.

If all the demand for family planning were met, the use of contraceptives in developing countries would rise from 51 percent to more than 60 percent. Such an increase would cause fertility to fall from the current average of four children per woman to about three, according to Steven Sinding of the Rockefeller Foundation. This decline would reduce the rate of population growth in the developing world (excluding China) from 2.3 percent per year to 1.6 percent, we estimate. An annual growth rate of 1.6 percent would mean that the population of the developing world would be 5.1 billion in the year 2025 instead of 6.5 billion.

It would cost an estimated $2.4 billion annually for family-planning programs to reach all the 120 million women whose potential demand remains unsatisfied. According to the United Nations Population Fund, the total current annual expenditures on family planning—including spending by couples, by the governments of developing countries and by donor organizations—is $4.5 billion. In 1992 the $325 million that the U.S. spent on population assistance amounted to less than 5 percent of its total expenditure on development aid.

Even if the percentage of women who use family planning does not increase, 100 million more couples will need to be served in the year 2000 than are served now, simply because the number of women of reproductive age is increasing as a result of past high fertility. As attitudes favoring smaller families continue to spread, the demand for family-planning services and thus the cost of supplying them will increase still further.

As the demographic data indicate, dramatic trends in family planning have emerged in developing countries. It would be unfortunate if the family-planning programs and the funding sources that support them failed to respond to the stunning changes in reproductive attitudes that have been observed in many Third World countries. Developed nations must make a substantial philosophical and financial commitment to meeting such needs. Otherwise, the reproductive revolution may be stymied.

FURTHER READING

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The Compton Gamma Ray Observatory

A steady stream of data from this orbiting observatory is painting a portrait of a dynamic and often enigmatic cosmos

by Neil Gehrels, Carl E. Fichtel, Gerald J. Fishman, James D. Kurfess and Volker Schönfelder

On April 5, 1991, the space shuttle *Atlantis* blasted off from the Kennedy Space Center in Florida carrying the 16-ton *Compton Gamma Ray Observatory* into space. Since then, the sophisticated satellite has been making the first comprehensive astronomical detections of gamma rays, the most energetic form of electromagnetic radiation. When viewed at gamma-ray energies, the universe appears unfamiliarly dynamic and capricious. *Compton*'s targets include some of the most violent objects in the cosmos: catastrophic supernova explosions, distant quasars expelling jets of gas that dwarf entire galaxies and gamma-ray bursts, flashes of gamma rays whose origin remains utterly unknown. Preliminary findings from *Compton* have particularly excited astrophysicists by shaking up many longstanding notions about the nature of those objects.

The reason for this rapid succession of surprises and discoveries is that *Compton*'s gamma-ray eyes are surveying nearly virgin scientific territory. Classical astronomy has depended entirely on observations of visible light, which constitutes a minuscule slice of the electromagnetic spectrum. Light consists of radiation having wavelengths between about 4,000 and 7,000 angstroms; in terms of the energy they carry, photons of visible light range from two to three electron volts. The earth's atmosphere completely absorbs all of the more energetic forms of radiation, ranging from far ultraviolet rays (those having more than about 10 electron volts) to gamma rays (those carrying anywhere from 10,000 to trillions of electron volts).

In their attempts to catch a glimpse of the gamma ray, groups of astronomers have spent the past two decades developing instruments that ride above the earth's obscuring atmosphere on board high-altitude balloons or on satellites. The *Compton Observatory* represents the grand culmination of that endeavor. Unlike earlier missions, *Compton* can detect photons over a broad band of energies—from 30,000 to 30 billion electron volts—and so the satellite can provide an exceptionally complete account of the objects that emit gamma rays. *Compton* is the first comprehensive gamma-ray satellite able to map the entire sky. Most important, the instruments on *Compton* provide about 10 times the sensitivity of previous gamma-ray detectors, along with greatly improved angular resolutions and timing capabilities.

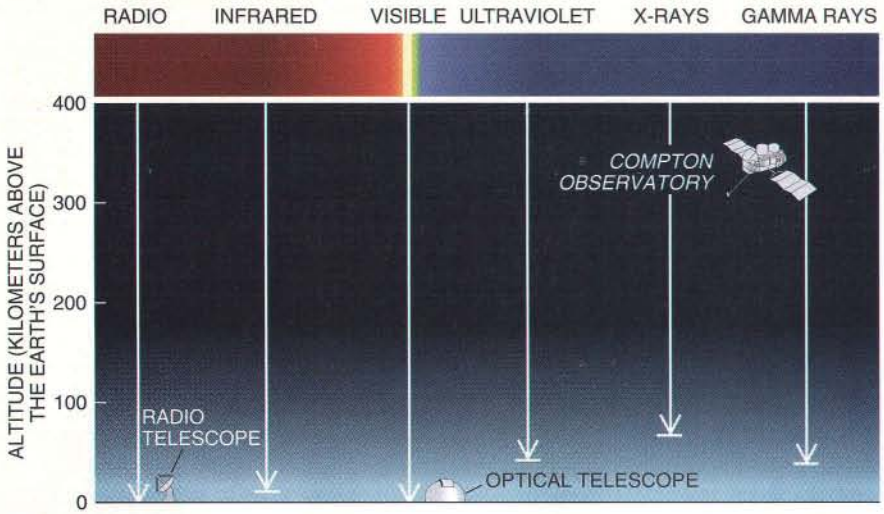
Compton's remarkable capabilities testify to the vast technological development and engineering effort that

NEIL GEHRELS, CARL E. FICHTEL, GERALD J. FISHMAN, JAMES D. KURFESS and VOLKER SCHÖNFELDER closely collaborate in collecting and analyzing data from the *Compton Gamma Ray Observatory*. Gehrels is an astrophysicist at the National Aeronautics and Space Administration Goddard Space Flight Center in Greenbelt, Md.; he is the project scientist for *Compton*. Fichtel is the chief scientist at Goddard's Laboratory for High-Energy Astrophysics and the acting head of the Gamma Ray Astrophysics Branch. He is also the principal investigator for the EGRET instrument on board *Compton*. Fishman heads the gamma-ray astronomy team at the NASA George C. Marshall Space Flight Center in Huntsville, Ala.; that team designed, built and operates the BATSE experiment. Kurfess heads the Gamma and Cosmic Ray Astrophysics Branch of the Naval Research Laboratory. He serves as the principal investigator for OSSE. Schönfelder is the head of the Gamma Ray Astronomy Group of the Max Planck Institute for Extraterrestrial Physics in Garching and is the principal investigator for the COMPTEL instrument.

went into its design. The satellite incorporates four synergistic instruments that operate in separate but overlapping energy ranges; each instrument specializes in different kinds of observations. The Burst and Transient Source Experiment (normally known by its acronym, BATSE) studies short-lived phenomena, such as gamma-ray bursts and solar flares. The Oriented Scintillation Spectrometer Experiment (OSSE) is ideal for measuring the low-energy gamma-ray spectrum of various celestial objects. The Imaging Compton Telescope (COMPTEL) generates images and collects spectra of sources that emit medium-energy gamma rays. Finally, the Energetic Gamma Ray Experiment Telescope (EGRET) gathers the highest-energy gamma rays.

Gamma rays cannot be reflected and focused like light, so the lenses and mirrors of conventional telescopes are useless for *Compton*. Instead the satellite's four instruments rely on technologies borrowed directly from the world of high-energy particle physics. BATSE and OSSE contain detectors composed of sodium iodide. When a gamma ray enters the sodium iodide, it excites the molecules and induces them to emit a flash of visible light, which is then recorded electronically. COMPTEL senses higher-energy gamma rays by using a layer of liquid gamma-ray-detecting material located above a layer of sodium iodide crystal. The instrument registers gamma rays that scatter in the liquid

***COMPTON GAMMA RAY OBSERVATORY* is the first satellite to make comprehensive observations of gamma rays that issue from celestial sources. From its vantage approximately 400 kilometers above the earth's surface, *Compton* maintains a round-the-clock surveillance of the gamma-ray sky. The orbiting observatory has already promoted new insights into the nature of quasars and confounded attempts to understand the objects responsible for gamma-ray bursts.**



ELECTROMAGNETIC SPECTRUM extends from feeble radio waves to extremely energetic gamma rays. Visible light makes up only a tiny part of the spectrum. Most electromagnetic rays, including gamma rays, are absorbed by atoms and molecules high in the earth's atmosphere. Astronomers have observed gamma rays by lofting instruments above the atmosphere on sounding rockets, on high-altitude balloons and on earth-orbiting satellites such as *Compton*.

detector and are then absorbed in the sodium iodide. This scattering process, in which gamma rays ricochet off electrons, was discovered in the 1920s by Arthur Holly Compton.

To capture the most energetic gamma rays, EGRET utilizes a design that differs significantly from those of the other instruments. EGRET contains numerous layers of electrified, fine-metal mesh, known as spark chambers. Incoming gamma rays produce pairs of electrons and positrons (antimatter twins to electrons) that give rise to short circuits between the wires. The resulting tiny sparks reveal the path that the gamma ray followed. A sodium iodide detector at the bottom of the instrument collects the electrons and positrons and measures their energy.

Three of the four instruments on *Compton* view very wide swaths of sky; they are pointed by turning the entire spacecraft. BATSE consists of eight units, one on each of *Compton*'s corners, that view the half of the sky that is not blocked by the earth. COMPTEL views a 64-degree-wide circular patch of sky; EGRET has a slightly smaller (45 degrees) field of view. In contrast, OSSE surveys a relatively small, four-by-11-degree area. It can quickly point toward and away from a particular gamma-ray source, thereby enabling researchers to subtract the background noise in OSSE's detectors from the source signal.

The rate at which gamma-ray photons are received from celestial sources is minute compared with the flux of photons of visible light. As a result, *Compton* must conduct lengthy scans in order to make meaningful gamma-ray measurements. On a typical observing run, *Compton* remains pointed in the same direction for two weeks. During that time, COMPTEL and EGRET collect data on one region in the sky, while BATSE continuously monitors gamma rays coming from all directions.

In its orbit 400 kilometers above the surface of the earth, *Compton* completes one circuit every 92 minutes; the earth blocks any given part of the sky for about one half of each orbit. Because OSSE points independently of the other instruments, it can switch to a second target while its first one is obscured by the earth.

In the two and a half years since its launch, *Compton* has contributed a cornucopia of astronomical discoveries. The most exciting observations concern the short-lived but brilliant blips of gamma radiation known as gamma-ray bursts. The nature of these bursts is one of the outstanding puzzles of modern astronomy. They are among the most prominent objects in the gamma-ray sky, and yet no one knows what they are, where they are located or what makes them burst [see "Gamma-Ray Bursters," by Bradley E. Schaefer; SCIENTIFIC AMERICAN, February 1985]. New data from *Compton* have raised only more questions about the nature of the objects that produce busts.

Gamma-ray bursts were discovered in the late 1960s by Ray W. Klebesadel and co-workers at Los Alamos National Laboratory, using detectors on the *Vela* satellites. Those satellites were designed to pick up gamma-ray flashes from nuclear detonations in order to monitor the Soviet Union's compliance with the Nuclear Test-Ban Treaty. *Vela* did discover short, potent bursts of gamma rays, but they originated in the heavens, not on the earth. The bursts occurred about a dozen times a year in what appeared to be random directions scattered over the whole sky. When the *Vela* data were declassified in 1973, the astronomical community immediately set out to determine the cause of these gamma-ray convulsions.

What has made the bursts so hard to understand is that after one ceases, it vanishes entirely. No unusual star or other steady object remains detectable where the burst occurred. When optical telescopes look in the direction of a burst, all that shows up is an ordinary patch of sky devoid of any noticeably peculiar objects. Furthermore, bursts do not all look alike. They last anywhere from one hundredth of a second to 1,000 seconds and differ in brightness by a factor of as much as 100,000. The most intense ones briefly outshine every other gamma-ray source in the sky combined, but it is impossible to ascertain the intrinsic luminosity of a burst without knowing its distance.

Before the launch of *Compton*, astronomers had arrived at a plausible and widely accepted explanation of the origin of bursts. According to the theory, bursts result from seismic disruptions, explosions or asteroid impacts on the surface of collapsed stellar remnants known as neutron stars. These stars have about the mass of the sun but are only 20 kilometers across; old, cool neutron stars would be almost impossible to detect using optical telescopes. The gravity on the surface of a neutron star is so powerful, however, that even a small disruption could unleash a brilliant outburst of gamma rays.

There is a simple way to test this model. Neutron stars, like most other stars in our galaxy, tend to lurk in the flattened disk that makes up the bulk of the Milky Way. Bursts should therefore appear to cluster in the sky along the plane of the Milky Way. Early measurements appeared to follow a more uniform distribution, but many astronomers chalked up those results to the poor sensitivity of the first gamma-ray detectors. The superior BATSE instrument on *Compton* was designed to pick up far fainter, more distant bursts. Like the dim stars that compose the shimmering band of the Milky Way, researchers expected that the faintest bursts seen by BATSE would nearly trace out the disk of our galaxy.

BATSE's findings have utterly con-

founded astronomers' expectations. For the past two years, the instrument has detected one burst a day, on average. But those bursts are absolutely uniformly spread across the sky. They display no sign of concentration along the galactic disk or in any other direction. At the same time, BATSE has discovered a distinct pattern in the brightnesses, and hence the distances, of the bursts.

If the objects that emit bursts were scattered evenly through space, the number of faint bursts should be systematically greater than the number of bright ones. The relation between brightness and number of bursts should follow directly from the fact that the apparent brightness of a burst decreases as the square of its distance, whereas the volume of space containing burst sources increases in proportion to the cube of the distance. BATSE discovered that the number of faint bursts falls off much faster than one would expect from that relation. The startling implication is that the satellite is seeing to the edge of the population of bursts; there is a shortage of faint bursts simply because few, if any, bursts lie beyond that edge.

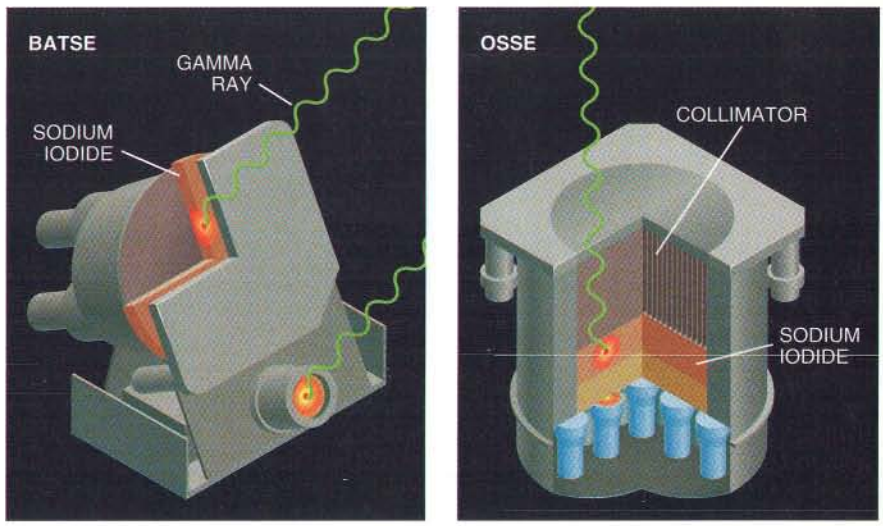
Taken together, the two key BATSE findings imply that the earth lies at the center of a spherical grouping of burst sources that extends only to a finite distance. Astronomers have been racking their brains trying to imagine what celestial objects might follow such a distribution.

Theorists have proposed many exotic explanations for the BATSE results. A few workers have suggested that the bursts result from collisions between comets or from other events lying just outside the planets in our solar system, but the mechanisms by which cometary collisions would generate gamma rays seem rather implausible. Another, more widely held possibility is that bursts occur on neutron stars that lie not in the disk of the galaxy but in a huge, outlying halo. Such models require elaborate ad hoc assumptions about the size and shape of the halo, however. They also raise the question of why neutron stars in the galactic disk do not produce significant numbers of bursts.

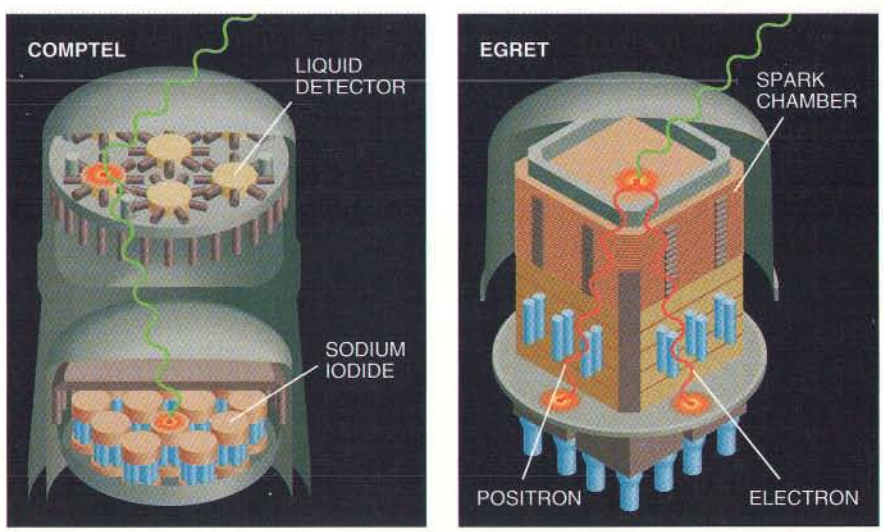
Some of the most intriguing theories hold that gamma-ray bursts originate in remote corners of the cosmos, perhaps when two orbiting neutron stars merge with each other or when a neutron star is devoured by a black hole. In these models the "edge" of the burst distribution would correspond to the finite size of the visible universe. If bursts truly take place in distant galaxies, they must be among the most energetic events in the universe.

A hand vote taken at a recent meeting of astrophysicists showed the community about equally divided between the galactic halo and the cosmological explanations. Only a small minority favored the models that place the bursts just outside the solar system. There are now well over 100 papers in leading astronomical journals describing possible solutions to the gamma-ray burst puzzle. Further detections by BATSE during the next few years may finally unveil the true character of these enigmatic objects. Many researchers are also hard at work searching for flashes of visible light that might appear in conjunction with a burst. Even a single such sighting would greatly help in weeding out the competing burst models.

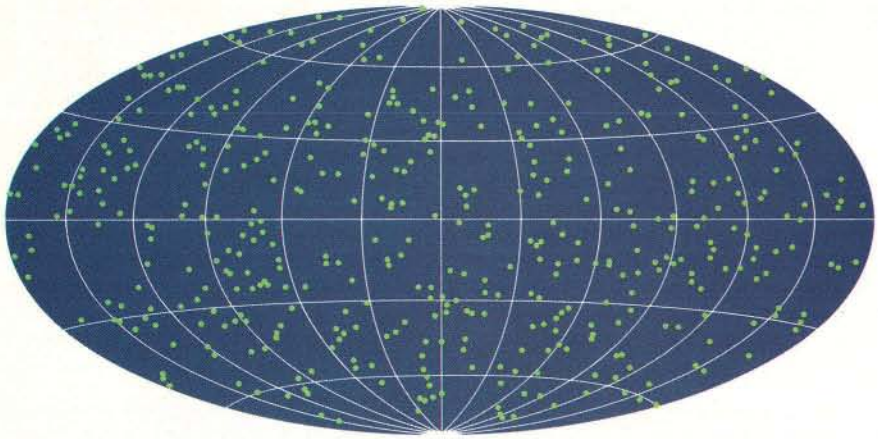
Whereas *Compton* has only intensified the puzzle of the gamma-ray bursts, it has elucidated the character of many other celestial phenomena. In particular, the satellite has improved our understanding of the nature of the bright and compact energy sources, collectively known as active galactic nuclei,



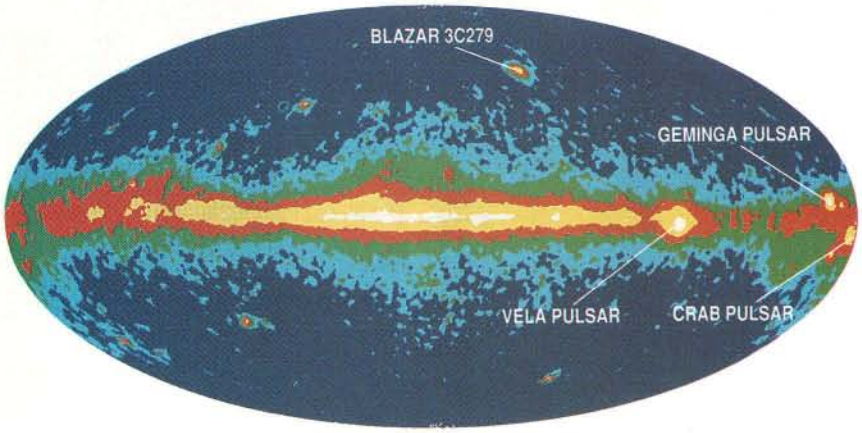
GAMMA-RAY DETECTORS often incorporate crystals of sodium iodide, a material that emits a flash of light when struck by a gamma ray. Sensitive light-detecting photomultiplier tubes collect that light and signal that a gamma ray has been observed. *Compton*'s BATSE instrument (*left*) consists of eight detectors that gather gamma rays from all parts of the sky. The OSSE instrument (*right*) contains a tungsten collimator and sodium iodide shielding that allow it to observe only a small patch of sky.



COMPTEL INSTRUMENT (*left*) uses two sets of detectors to capture gamma rays. An incoming gamma ray scatters off an electron in the liquid detector at the top and continues on into a block of sodium iodide, where it is absorbed. In both detectors, the gamma ray produces a recordable flash of light. In the EGRET instrument (*right*), extremely energetic gamma rays create pairs of electrons and positrons. These particles instigate short circuits in a series of electrified grids, or spark chamber, before depositing their energy into a sodium iodide crystal.



GAMMA-RAY BURSTS (*green dots*), as seen by BATSE, appear to cover the sky uniformly. Contrary to most astronomers' expectations, the bursts do not concentrate toward the band of the Milky Way (*central horizontal line*) or toward any known galaxy or cluster of galaxies. This distribution indicates that the burst sources are evenly spread in all directions, perhaps because they occur in distant galaxies.



GAMMA-RAY SKY MAP produced by EGRET shows that the constant gamma-ray glow appears brightest along the plane of the Milky Way. The diffuse emission primarily originates from energetic interactions between cosmic rays and the atoms and particles strewn between the stars. Several nearby pulsars and brilliant, distant quasars are also visible. White indicates the most intense emission, dark blue the least.

that lurk in the centers of some galaxies. Roughly 1 percent of all galaxies have active nuclei, although as many as 30 percent display some evidence of an agitated zone at their center. In the case of quasars (which are among the most luminous of active galactic nuclei), a region only slightly wider than our solar system greatly outshines the entire surrounding galaxy.

Most astronomers believe a supermassive black hole—a collapsed object containing millions to billions of times the mass of the sun—is the culprit responsible for the great outpourings of energy from active galactic nuclei. The black hole's concentrated gravitational pull draws in nearby stars and tears them asunder. Before the disrupted matter disappears into the black hole, it forms a disk and grows extremely hot. The hot gas in the disk releases tremendous amounts of electromagnetic radiation, ranging from low-energy radio waves to gamma rays. In some cases, elementary particles (such as electrons and positrons) shoot away from the disk in narrow, magnetically confined jets that move at nearly the speed of light. These particles emit radiation that makes the jets detectable to astronomers. When the jets point toward the earth, the object is classified as a blazar.

Active galactic nuclei come in two basic varieties: those that are strong radio sources and those that are not. Nearly all blazars are intense radio sources. In general, radio-loud sources reside in elliptical galaxies, whereas radio-quiet ones are found in a class of active spiral galaxies known as Seyfert galaxies.

Compton has revealed that the two classes of active galactic nuclei have very dissimilar gamma-ray signatures as well. OSSE and COMPTEL have found that the gamma-ray emission from Seyfert galaxies cuts off at energies above 100,000 electron volts. In contrast, EGRET discovered that many of the radio-loud blazars shine all the way up to the highest energies that the instrument can detect. The instrument also gave scientists a newfound sense of the incredible amount of energy radiated by these objects.

In June 1991, EGRET detected its first two blazars: 3C273, located 1.8 billion light-years from the earth, and 3C279, which appears close to 3C273 in the sky but which lies 4.6 billion light-years away. Amazingly, 3C279 appeared by far the brighter of the two. Despite its great distance, 3C279 shines as one of the brightest sources in the high-energy gamma-ray sky. To be so bright, the blazar must emit thousands of times as much energy in the form of gamma rays as does the Milky Way across the entire spectrum.

The blazar 3C279 turned out to hold more surprises for *Compton* scientists. During a two-week period in June 1991, EGRET watched 3C279 slowly brighten by a factor of two; the object then dimmed by a factor of four in only two days. Such rapid variability indicates that the size of the region in which the gamma rays are created is very small. Evidently, a physical change was able to travel across the source region, causing a significant change in its gamma-ray emission, in no more than a few days. By inference, the source region can be no larger than a few light-days across, only several times the diameter of Pluto's orbit around the sun.

EGRET has since detected 26 gamma-ray-emitting active galactic nuclei. Like 3C279, almost all these objects are classified as blazars. These gamma-ray-emitting blazars reside at distances ranging from 400 million to nine billion light-years away. The most remote of these are being seen nearly out to the visible limit of the universe (which we assume, in this article, to be 13 billion light-years distant).

The current best explanation of why blazars are such strong gamma-ray sources is that the gamma rays originate in jets that point toward the earth. In the jets, low-energy photons (such as light or ultraviolet rays generated in the disk around the black hole) would often bounce off rapidly moving electrons. Through this process the photons could gain enough energy to become gamma rays and would align with the particles in the beam. Because the

resulting radiation would concentrate along a narrow beam, the blazar would appear especially brilliant if the beam happened to point earthward. For years, researchers have speculated that jets might strongly affect the emissions from some active galactic nuclei; the EGRET results seem to confirm the theory.

Another phenomenon that can light up the gamma-ray sky is a supernova, the cataclysmic explosion that marks the end of the life of a massive star. Supernova explosions have strongly influenced the chemical evolution of the universe. According to the big bang model of cosmology, the universe initially was composed entirely of hydrogen and helium. All heavier elements—including the carbon in our bodies and the silicon and iron that make up much of the earth—have been created through nuclear fusion reactions in the interiors of stars. Supernovae provide the primary mechanism by which these elements recycle into interstellar space, where they are incorporated into the next generation of stars and, presumably, planets. Stable stars do not create elements, such as gold, that are heavier than iron; these atoms form only in the extreme temperatures and densities that prevail in a supernova detonation.

On February 23, 1987, astronomers received a marvelous opportunity to learn more about the process by which supernovae form new elements. At that time, a nearby supernova, dubbed Supernova 1987A, exploded in the Large Magellanic Cloud, one of the Milky Way's satellite galaxies [see "The Great Supernova of 1987," by Stan Woosley and Tom Weaver; SCIENTIFIC AMERICAN, August 1989]. Supernova 1987A was the nearest and brightest supernova visible on the earth since the invention of the telescope nearly four centuries ago; researchers quickly trained all available space-based and earthbound instruments on this remarkable object.

The supernova began its life as a blue star having about 20 times the mass of the sun. During the explosion, swift nuclear reactions produced a number of rare, short-lived radioactive nuclei, in addition to other, more stable heavy elements. Some of these radioactive nuclei emit gamma rays having distinctive energies when they decay. The most easily detected of these are the gamma rays emitted by cobalt 56 (which decays into iron 56) and by cobalt 57 (which likewise decays into iron 57). Many of these gamma rays are absorbed in the expanding cloud of gas produced by the supernova; after being scattered and rescattered, the rays may eventually emerge as visible light.

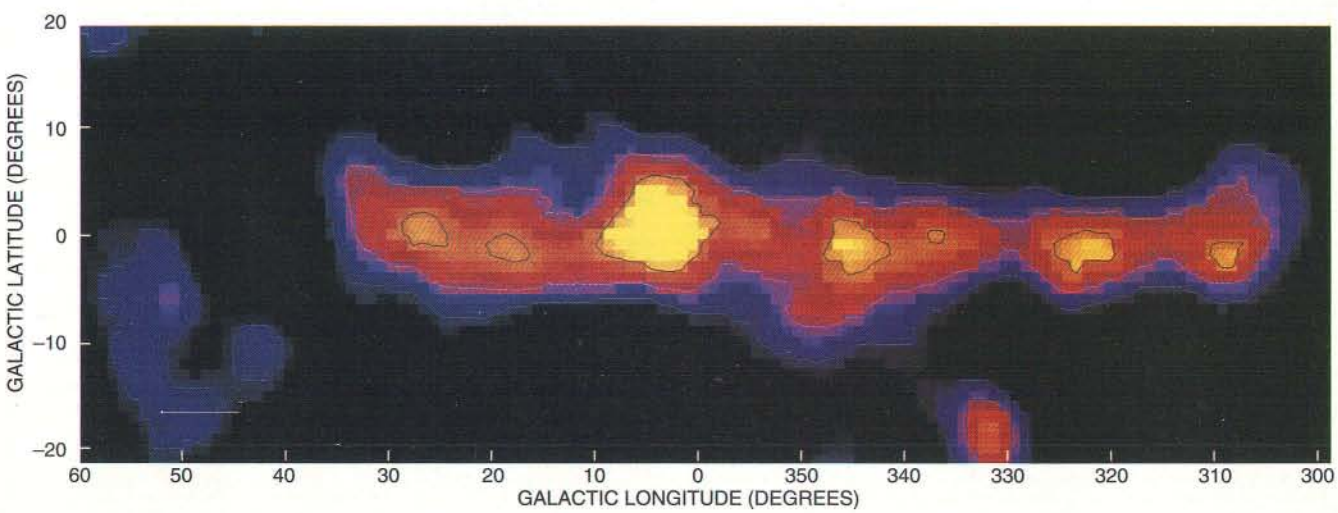
Even before Supernova 1987A, several theorists (including Donald D. Clayton of Clemson University, Stirling A. Colgate of Los Alamos National Laboratory and Stanford E. Woosley of the University of California at Santa Cruz) had thought about the role of radioactive isotopes in supernova explosions. Some workers noted that radioactive decays could serve as a primary source of energy that keeps the expanding supernova visible; others pointed out that some of the associated gamma rays might penetrate the cloud of debris and hence be directly detectable.

Observations of Supernova 1987A stunningly confirmed the prediction. Cobalt 56 has a half-life of 77 days; from 1987 through 1990, the visible light from the supernova faded at exactly that rate. The *Solar Maximum Mission* satellite and instruments on National Aeronautics and Space Administration research balloons also detected gamma rays from the supernova carrying 847,000 and 1,238,000 electron volts. These are precisely the energies associated with the decay of cobalt 56.

Since 1991 the visible light from Supernova 1987A has faded at a rate corresponding to a half-life of about 270 days, the exact half-life of cobalt 57. It seems that cobalt 57 is now the main radioactive isotope powering the supernova. OSSE has followed up on the previous observations by detecting the 122,000-electron-volt gamma rays characteristic of the decay of cobalt 57. The comparative intensities of the gamma-ray emission from the two forms of cobalt reveal the ratio of nickel 57 to nickel 56 created in the supernova. The ratio from the supernova is close to the measured ratio in the sun. That match offers impressive confirmation that supernovae are responsible for producing most of the heavier elements found in the sun and throughout the universe.

Other radioactive elements generated in supernova explosions have much longer lifetimes than do cobalt 56 and cobalt 57. The fairly abundant radioactive isotope aluminum 26, for instance, has a half-life of 716,000 years. Supernova explosions occur once every 30 years or so in the Milky Way, so the aluminum 26 from about 24,000 supernovae (716,000 divided by 30) should be dispersed throughout our galaxy.

Gamma-ray astronomy offers an efficient way to locate aluminum 26 and hence to identify the places where new elements are being synthesized. In ad-



RADIOACTIVE NUCLEI of aluminum 26 permeate the Milky Way. The aluminum 26 is thought to originate mostly in supernova explosions, where rapid nuclear reactions build up a wide variety of heavy atomic nuclei. As aluminum 26 decays, it emits gamma rays having the distinctive energy that is singled out in this COMPTEL image. The bright lumps show unexpected concentrations of newly synthesized nuclei in addition to the anticipated concentration along the galactic plane.

dition to supernovae, less powerful nova explosions and certain violently active stars may create aluminum 26. When aluminum 26 decays, it gives rise to gamma rays having energies of 511,000 and 1,809,000 electron volts (as well as rays at several other energies). *Compton* can map the location and intensity of the spots along the band of the Milky Way where those gamma rays originate. Gamma rays have such incredible penetrating power that they easily zip through the gas and dust that obscures optical views of the galaxy, so *Compton* can see all of the aluminum 26 in the entire galaxy.

COMPTEL has recently completed the first detailed map of aluminum 26 in the Milky Way. As we expected, the aluminum 26 appears concentrated along the band of the Milky Way, as are most stars and supernovae. But we and our colleagues were surprised to see that the map is mottled with bright spots and intervening regions emitting fewer gamma rays. The significance of the bright spots remains unknown. Perhaps they are regions of massive star formation, individual nearby supernova remnants or some phenomenon that we and our colleagues have not yet been clever enough to think of.

The aluminum 26 image, along with more precise ones still being prepared, will serve as a long-awaited galactic road map for high-energy astrophysicists. COMPTEL has just filled in another detail of the galactic landscape by observing gamma rays from Cassiopeia A, the remnant of a supernova that exploded in 1668. The instrument seems to have detected the telltale gamma-ray signature of titanium 44, which has a half-life of 54 years. By homing in on gamma rays from titanium 44, *Compton* may be able to pick out other recent supernovae that have been hidden from view by clouds of gas or dust.

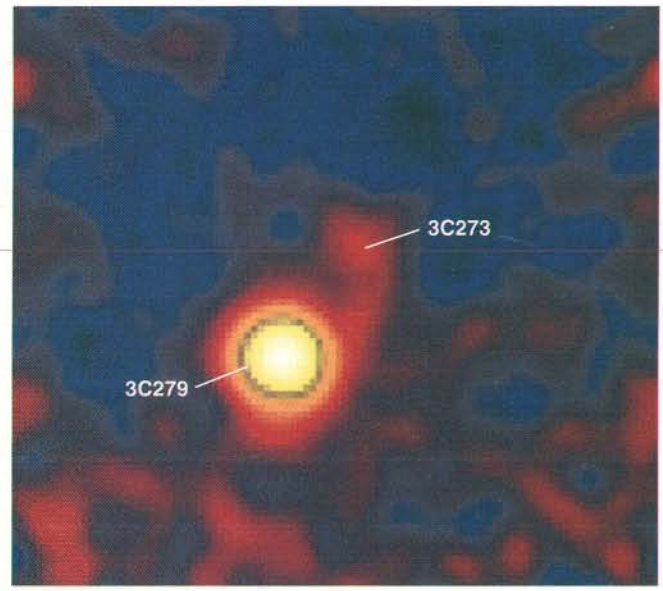
The 511,000-electron-volt gamma rays associated with the decay of cobalt 56 and aluminum 26 have an exotic origin. They trace their genesis to the positrons that are ejected when those isotopes decay. When a positron encounters an electron, the two particles annihilate each other and produce pure energy in the form of gamma radiation. This annihilation is the ultimate proof of Albert Einstein's famous concept that mass can be converted into energy in accordance with the equation $E = mc^2$.

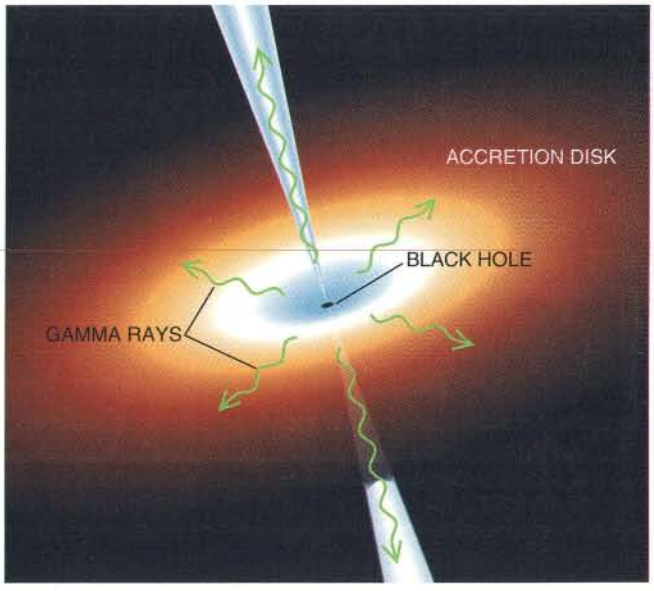
OSSE has detected a strong flux of 511,000-electron-volt gamma rays coming from the central region of the Milky Way. We are convinced that these gamma rays result from the annihilation of electrons and positrons but cannot yet say for certain what objects are making the positrons. Some of them may derive from the radioactive elements cooked up in the numerous supernova remnants scattered in the galaxy's inner regions. Several researchers have argued that some of the annihilation radiation comes from one or more discrete sources, possibly stellar-mass black holes. High-resolution maps of the distribution of the annihilation radiation along the Milky Way should help unmask the origin of these gamma rays [see "What Is Happening at the Center of Our Galaxy?" by Charles H. Townes and Reinhard Genzel; SCIENTIFIC AMERICAN, April 1990].

Compton has elucidated another aspect of the aftermath of a supernova explosion. Whereas most of the exploded star expands outward as a radioactive cloud, the star's iron core implodes to form a compact neutron star or, in the most extreme cases, a black hole. Neutron stars essentially are made of nuclear matter without any empty space; a teaspoonful of neutron star would weigh more than a billion tons. As the core collapses, its rate of rotation increases enormously because of conservation of angular momentum (as in the familiar analogy of the skater pulling in her arms to make herself spin faster on the ice). Consequently, the neutron star may end up rotating hundreds of times per second. The drastic shrinking of the star also greatly magnifies the strength of its magnetic field, elevating it to trillions of times the strength of the earth's field.

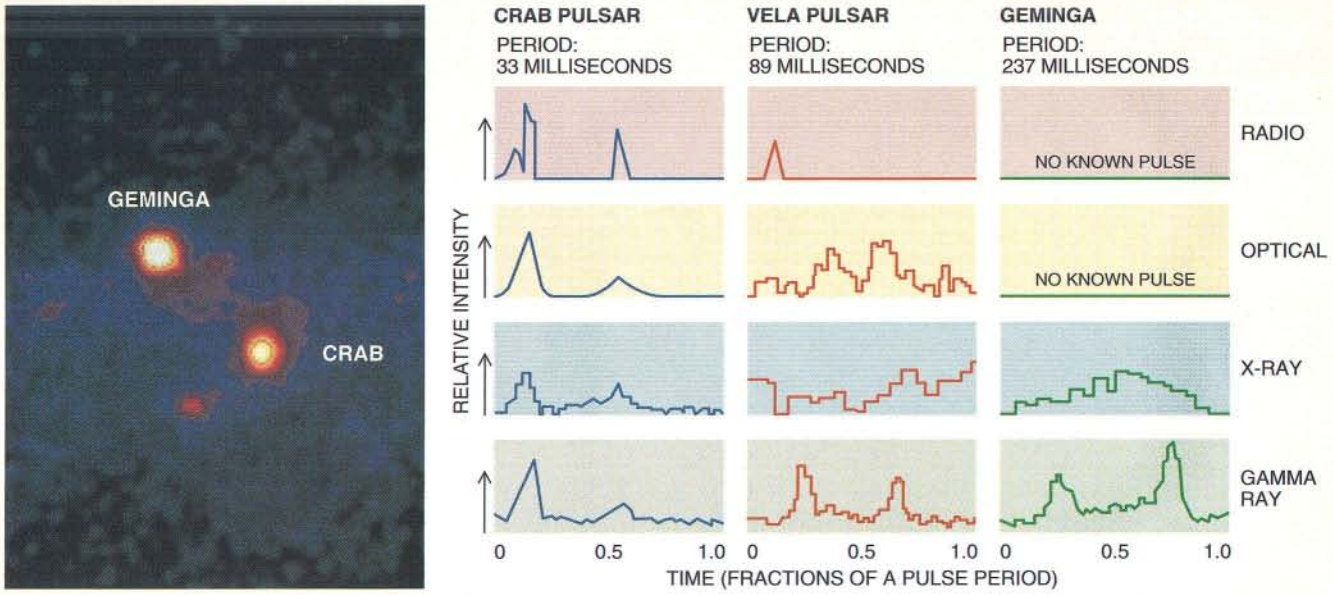
The rapidly spinning neutron star acts as a giant particle accelerator. Subatomic particles trapped in the star's magnetic field are whipped around until they attain velocities very close to the speed of light. These energetic, electrically charged particles give rise to cones of radiation that rotate with the star, somewhat like the beams of light from a lighthouse. As the cones sweep across the earth, astronomers see the neutron star blink on and off.

This blinking activity was first noticed in 1967, when Antony Hewish and Jocelyn Bell and their co-workers at the





BLAZAR 3C279 (*left*) shines prominently in this EGRET image, despite being some five billion light-years distant. The nearer but fainter blazar 3C273 appears at the upper right. Quasars are thought to derive their tremendous energy from gas falling into a black hole having millions to billions of times the mass of the sun (*right*). Jets of charged particles that shoot out perpendicular to the disk of gas may give rise to brilliant, focused beams of gamma rays.



FLASHES OF RADIATION emanate from pulsars, rapidly spinning stellar masses only 20 kilometers across. Young pulsars shine prominently at gamma-ray energies (*left*). The graphs (*right*) show variations in the brightness of pulsars as seen in different regions of the electromagnetic spectrum. For poorly understood reasons, some pulsars appear synchronized in all parts of the spectrum, whereas others are staggered; Geminga does not show up at all in radio telescopes.

University of Cambridge discovered radio sources that pulsed in a fast, extremely regular fashion. Because of their behavior, these spinning neutron stars are known as radio pulsars. Researchers later learned that some pulsars can be detected at much higher energies as well.

Of the 500 known radio pulsars, only two—the Crab and Vela pulsars—had been detected at gamma-ray energies by instruments predating *Compton*. Since its launch, *Compton* has detected four more gamma-ray pulsars: the Circinus pulsar, PSR 1706-44, PSR 1055-52 and Geminga (the numbers refer to the sky coordinates of the pulsars). As has happened every time *Compton* has examined a new kind of target, gamma-ray observations of pulsars have revealed peculiar traits that expand and challenge current theory.

Pulsar researchers often analyze such bodies by comparing their light curves in different parts of the electromagnetic spectrum. The light curve plots how a pulsar's brightness changes over the course of one of its rotations. A look at the light curves of the six known gamma-ray pulsars shows that each pulsar has a unique radiation signature. The Crab, for example, emits two pulses per rotation (like a lighthouse); the pulses occur synchronously at many energies. The Vela pulsar follows different patterns depending on the energy at which one watches it. Both the Crab and Vela display pulsations in visible light, but no other pulsar does. Then there is the oddball Geminga, which radiates strongly at gamma-ray energies but, unlike every other pulsar known, cannot be detected by radio telescopes.

Geminga may in fact represent the first of a new class of pulsars that do not have radio pulsations. We are searching through the data from *Compton* for evidence of other such gamma-ray pulsars. Geminga's radio silence may indicate that its beam of radio emission is more narrowly focused than its gamma-ray beam, so that the radio pulses miss the earth as the star spins around. *Compton* has provided some support for this explanation; for example, the radio pulses from the Crab appear distinctly narrower (that is, shorter in duration) than those detected at gamma-ray energies.

A noteworthy piece of information gleaned from the newly discovered gamma-ray pulsars is that old, slowly rotating neutron stars create gamma rays much more efficiently than do young ones. Researchers estimate the age of a pulsar by measuring how quickly its period of rotation changes over the years. The rotation period gradually increases because the radiation emitted by a pulsar slowly siphons away its angular momentum. The relation between the pulsar's period and the rate of deceleration of its rotation can reveal approximately how long ago the pulsar was born in a supernova explosion.

To calculate the gamma-ray efficiency of a pulsar, astronomers divide the object's energy output in gamma rays by the total energy loss of the system as inferred by its changing period. Amazingly, Geminga and PSR 1055-52 seem to emit almost all their energy in the form of gamma rays. How they accomplish this feat is still unknown, but from our gamma-ray point of view, pulsars are objects that improve with age.

The results presented here offer just a small sample of the wealth of data obtained by the *Compton Observatory*. Most gamma-ray phenomena in the sky are transient or variable, so many wondrous discoveries may yet await *Compton*. Already the satellite has expanded human consciousness beyond our traditional, light-centered view of the universe. We anticipate that the observatory will continue to operate for another five to 10 years. The fun in gamma-ray astronomy is just beginning.

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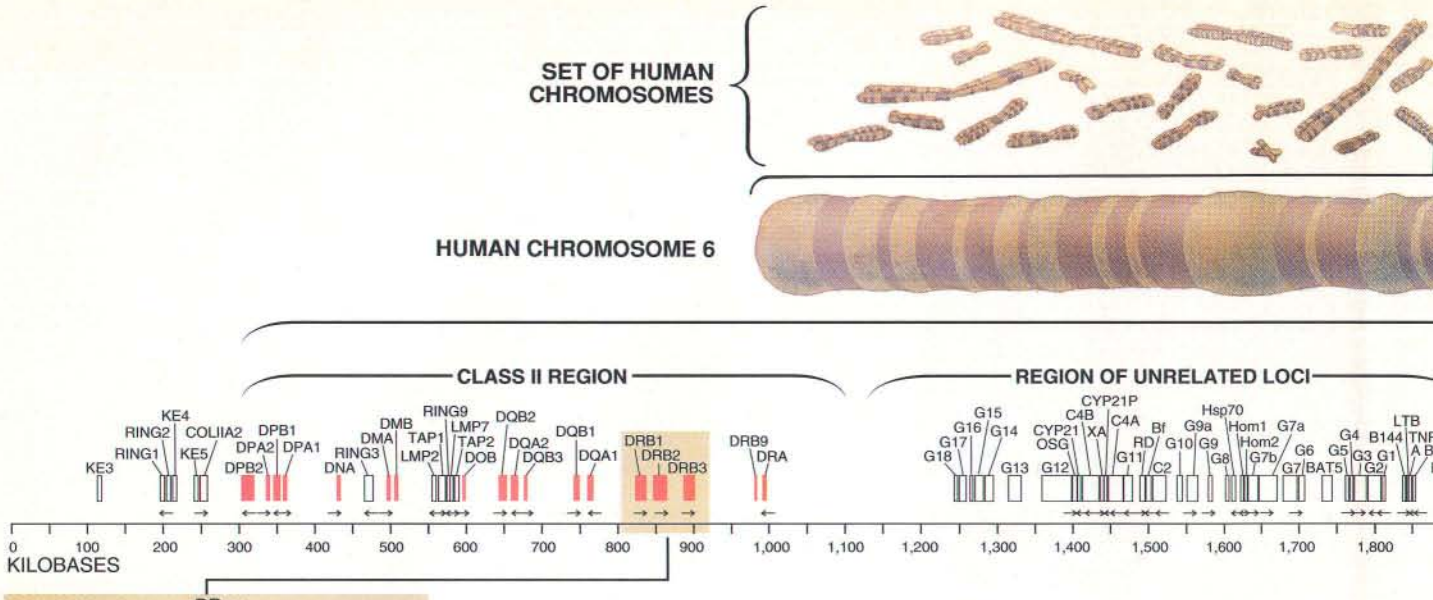
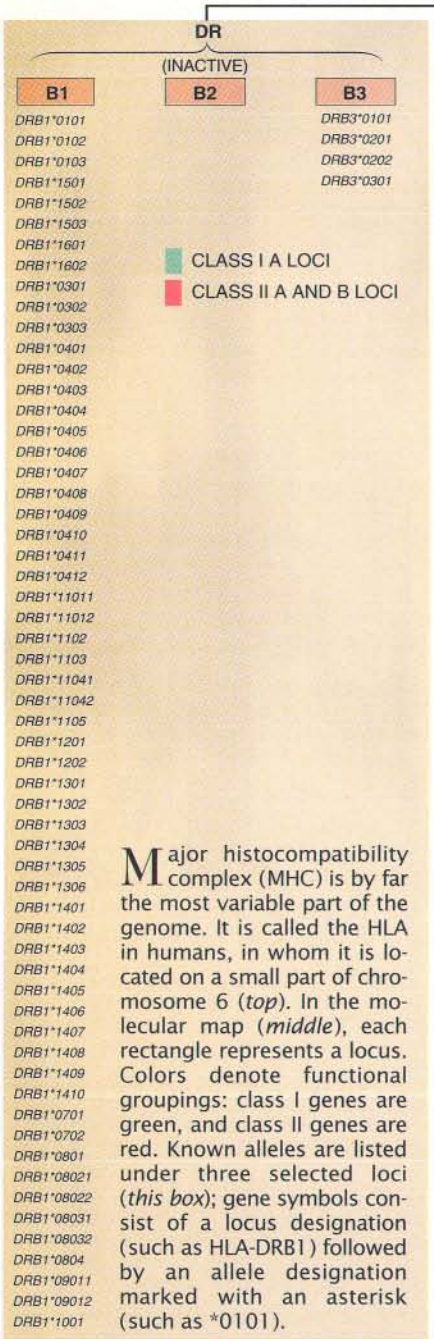




Major histocompatibility complex (MHC) is by far the most variable part of the genome. It is called the HLA in humans, in whom it is located on a small part of chromosome 6 (*top*). In the molecular map (*middle*), each rectangle represents a locus. Colors denote functional groupings: class I genes are green, and class II genes are red. Known alleles are listed under three selected loci (*this box*); gene symbols consist of a locus designation (such as HLA-DRB1) followed by an allele designation marked with an asterisk (such as *0101).

MHC Polymorphism and Human Origins

The diversity of human tissue types was generated long before Homo sapiens *emerged*

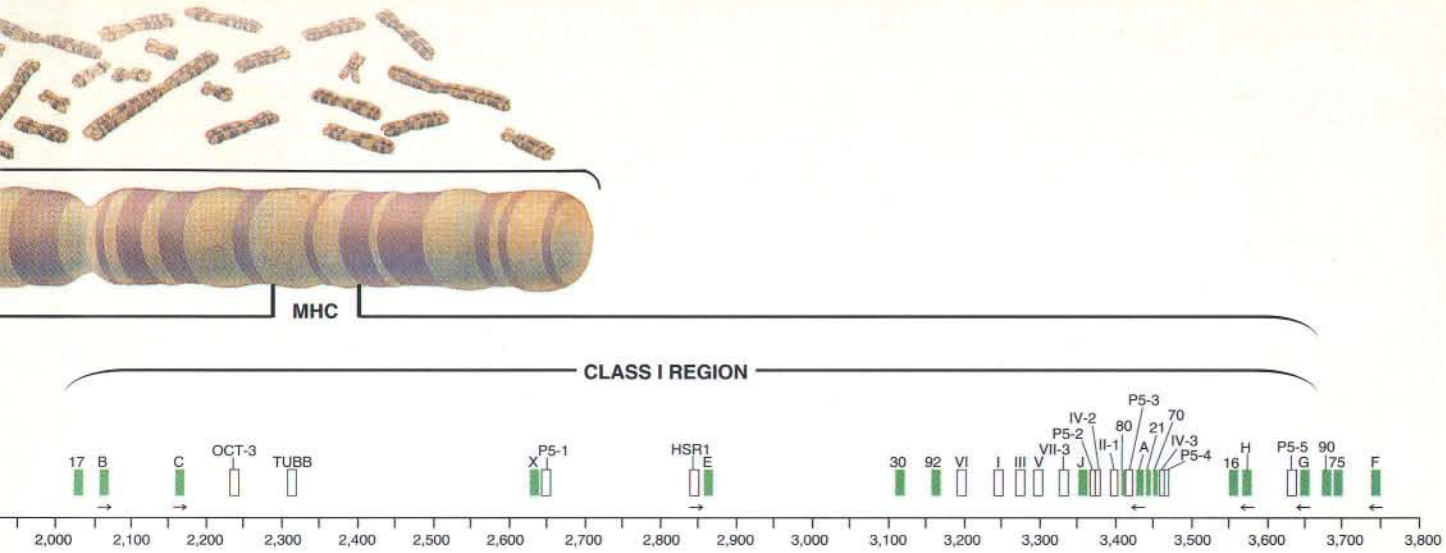
by Jan Klein, Naoyuki Takahata and Francisco J. Ayala

Did the human species emerge from a handful of individuals, perhaps even from a single woman? Or did it arise from a large group, having perhaps as many as 10,000 members? Some recent studies favor the view that our species and others originated in small ancestral populations. Yet an inquiry into the evolution of the genes that control the immune system's capacity to recognize foreign proteins has produced grounds to dissent from this view. To understand the matter, it is helpful to review the immune system, its method of recognizing invaders and the genes that control it.

The story begins more than half a century ago with the English pathologist Peter A. Gorer, then at University College, London. Gorer discovered that each body parades a regalia of molecular markers on the surface of most of its cells, which differentiate individuals of the same species from one another. Because they determine tissue compatibility—the capacity to accept a graft from another individual—they were termed histocompatibility molecules. He further demonstrated that among the many histocompatibility molecules, one set has a predominant influence on tissue compatibility. This set is specified by a long array of genetic loci occupying a single region of a chromosome—the major histocompatibility complex (MHC).

We now know that the physiological function of MHC molecules is not to thwart the noble efforts of the transplant surgeon but to initiate an immune response to parasites. While they are being manufactured in the cell, the MHC molecules bind short peptides and display them on the cell surface. Most of the peptides are derived from the body's own proteins (self-peptides), but when the body is infected by a parasite, the assembling MHC molecules also pick up peptides derived from the broken-down proteins of the invader (nonself-peptides).

Certain lymphocytes, the *T* cells, continually scan the surfaces of other cells, ignoring those displaying self-peptides but locking onto those whose MHC molecules display nonself-peptides. The *T* cells do so because they have receptors



that are complementary to the particular combination of self-MHC molecules and nonself-peptides. The *T* cell receptors recognize this assembly, the recognition activates the lymphocytes, and the activated lymphocytes then set into motion a complex array of mechanisms aimed at destroying the invaded cell and the invader itself. In the case of grafted tissue, on the other hand, the *T* cells recognize as foreign the MHC molecules of the donor, which are different from those of the host, and the immune attack is then directed against the transplant.

The human MHC, referred to as the human leukocyte antigen (HLA) complex, contains more than 100 genes and occupies a chromosomal region more than four million base pairs in length. Only some of these genes encode molecules involved in the presentation of peptides to *T* lymphocytes. Others include genes that control the degradation of proteins into peptides and transport of the peptides across membranes; genes that specify other components of the immune system; genes that subserve functions that are either unknown or unrelated to the immune response; and nonfunctional genes.

The MHC genes proper fall into two classes, I and II, distinguished both structurally and functionally. Here we shall focus on DRB1, one of the functional class II genes found in humans and other primates. Most of the conclusions we reach from the analysis of the DRB1 genes, however, apply also to other functional MHC genes.

The fact that tissue grafts are invariably rejected by the host whenever they are contributed by an unrelated donor suggests that we all differ in our MHC molecules. This suggestion is borne out by sequencing of MHC genes, which has revealed that each of the functional MHC loci can be occupied by one of many alleles. (A locus can be compared to the date-display window of a calendar watch, with the dates representing the different alleles.) Because there are several functional MHC loci on a given chromosome and each locus has many alleles, numerous allelic combinations (at least 10^{12}) are theoretically possible.

Only a fraction of the possible combinations actually occurs in the human population. Yet even this fraction is large enough to ensure that virtually no two randomly chosen, unrelated individuals will have the same MHC alleles at all of their MHC loci. This situation strikingly contrasts with that in other genetic systems, in which each locus has either one allele only (that is, the display window is stuck on one date) or a low number of alleles at a locus, of which one is common and the others are rare. The existence of multiple alleles at a locus, each allele occurring at an appreciable frequency in a population, is termed polymorphism.

The high number of alleles is, however, only one of two extraordinary features of the MHC polymorphism. The other is the large nucleotide diversity among the MHC alleles. In other genetic systems, alleles at a given locus usually differ by a few nucleotide substitutions at most. In the MHC, some alleles differ by 100 or more substitutions.

Now to speciation, the process by which a parental species gives rise to daughter species: if it were true that new species emerge from a small number of founding individuals or, in the extreme case, a single pregnant female, then polymorphisms should arise anew after each speciation. In other words, polymorphism should be younger than the species. One can easily appreciate why this should be so by imagining a bag with 20,000 marbles of 40 different colors, each color represented equally. If one draws 100 marbles at random from the bag, there is a very low probability—0.02, to be precise—that the sample will contain all 40 colors.

A more precise argument for a relatively young age of polymorphism is provided by the coalescence theory of population genetics. Like kings and aristocrats, genes, too, can be envisioned as having pedigrees. The genealogy of any two neutral genes randomly chosen from an extant population can theoretically be followed back in time until it coalesces in a single ancestral gene. (A gene is considered "neutral" when it does not confer a selective advantage in comparison with other genes.) The mean number of generations necessary to trace the lineages back to the coalescent gene is equal to twice the effective population size, or roughly twice the number of breeding

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individuals. Hence, assuming a past effective population size of 10,000 individuals and a mean generation time of 20 years, the mean coalescence time of two neutral genes now present in the human population is 400,000 years. As archaic *Homo sapiens* is currently believed to have emerged more than 500,000 years ago, most of the polymorphism of the human species should have been generated since then.

If this conclusion were also to apply to MHC genes, one would have to postulate that they have a much higher mutation rate than do other genes. Only in this way could they have accumulated, during the same time span, so much greater an extent of polymorphism. In fact, some 15 years ago this was indeed the consensus view of MHC polymorphism. To one of us (Klein), however, this consensus did not seem to square with the observations.

In the late 1970s Bernhard Arden, Edward K. Wakeland and Klein, all then working at the Max Planck Institute for Biology in Tübingen, found identical MHC alleles in two mouse species that had diverged two million years ago. This quite unexpected finding, in species whose MHC diversity at least matches that of humans, implied that the MHC genes did not evolve faster than other genes.

In 1980 Klein proposed that the extensive nucleotide diversity of the MHC alleles stemmed not from a high mutation rate but from widespread transmission of MHC polymorphism from parental to daughter species. According to this transspecies hypothesis, most of the MHC alleles make it through the period of speciation, just as family jewelry is handed down from generation to generation. Therefore, the mean coalescence time of MHC alleles can be much longer than the life span of a species [*see bottom right illustration on page 50*].

The first direct evidence supporting the transspecies hypothesis emerged in 1988, when investigators began to compare sequences of MHC alleles from related species. Klein and Felipe Figueroa of the Max Planck Institute in Tübingen, in collaboration with Eberhardt Günther of the University of Göttingen, demonstrated the existence of alleles that had diverged before the separation of the evolutionary bloodlines leading to the house mouse and the Norway rat, an event currently dated at more than 10 million years ago. Evidence for the antiquity of MHC alleles in rodents and primates has also been found in the laboratories of Wakeland, now at the University of Florida at Gainesville, Werner E. Mayer of the Max Planck Institute in Tübingen, Peter Parham of Stanford University, Henry A. Erlich, then at the Cetus Corporation in Emeryville, Calif., Ronald E. Bontrop of ITRI-TNO in Rijswijk, the Netherlands, and others.

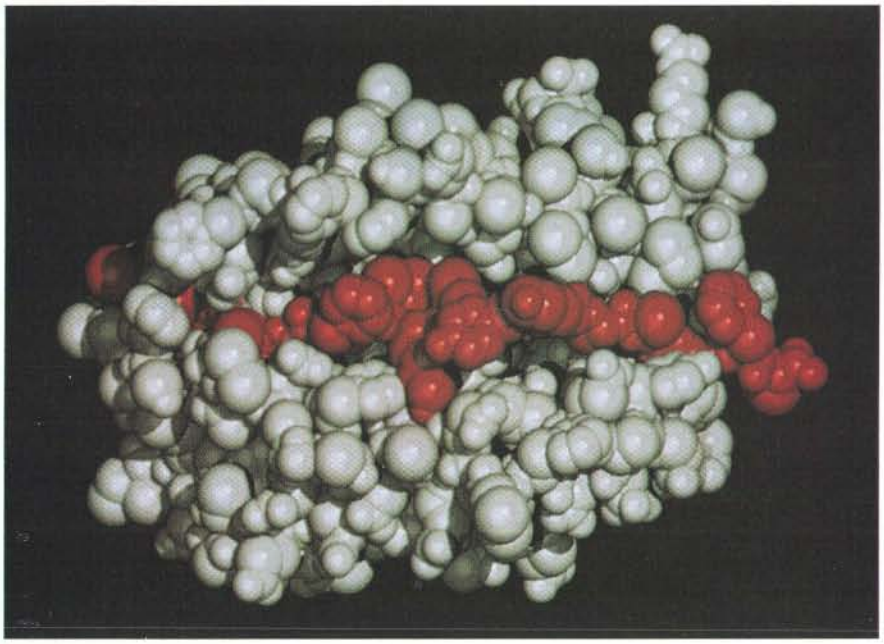
An example of a transspecies polymorphism is furnished by two human alleles at the DRB1 locus, which differ more from each other than from the corresponding alleles in the chimpanzee. The relations can be measured precisely in terms of genetic distances, that is, the number of nucleotide substitutions divided by the number of sites compared. A family tree of the four alleles can be constructed in which these distances are proportional to the length of the branches, and genes with the shortest distances between them are neighbors [*see bottom left illustration on page 50*].

The tree indicates that the two human alleles diverged from a common ancestral gene before the ancestors of the human and chimpanzee species separated from each other more than four million years ago. Klein, Figueroa and Colm O'hUigin of the Max Planck Institute in Tübingen obtained evidence that certain other human MHC alleles diverged before the separation of prosimian and anthropoid primates more than 65 million years ago. During this period, there must have been many speciation events, and the MHC polymorphism must have been passed on through all of them.

The antiquity of MHC allelic lineages contradicts the coalescence theory's conclusion that all human alleles date back no further than 400,000 years. One of us (Takahata) suggested in 1990 that the difficulty lies in the theory's main premise, namely, that the genes in question are not neutral but subject to balancing selection—a form of selection that keeps two or more alleles in a population longer than would be expected if they were drifting in random manner. In extending the theory to genes under selection, Takahata demonstrated that coalescence time varies in proportion to the intensity of selection: the stronger the selection, the longer it takes two gene lineages to coalesce. His calculations yield mean coalescence times of many millions of years.

Indirect evidence that functional MHC genes are under balancing selection has been provided by Austin L. Hughes and Masatoshi Nei, both then at the University of Texas Health Science Center at Houston. The evidence is based on the distinction between nucleotide substitutions that do not change the identity of the specified amino acids (referred to as synonymous) and those that do (nonsynonymous). Because mutations affect synonymous and nonsynonymous sites equally, the ratio between the two types of substitution—a parameter we call gamma—should be equal to one, provided the substitutions are selectively neutral.

Synonymous substitutions are generally neutral. But nonsynonymous substitutions may confer an advantage, resulting in "positive selection" that yields



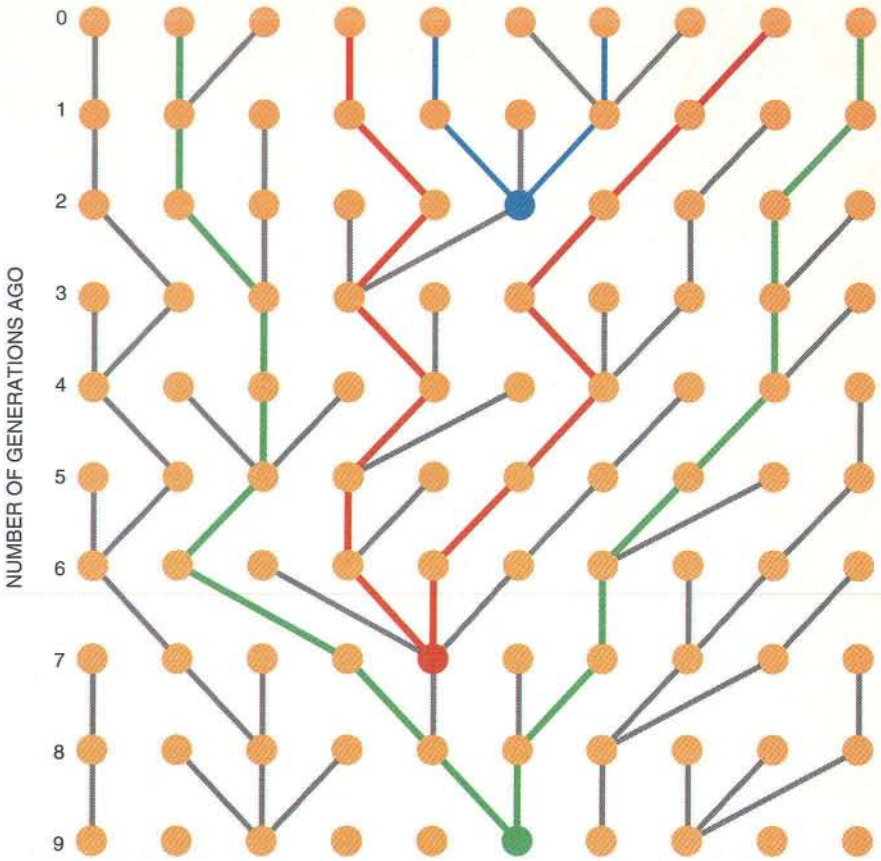
IMMUNE RESPONSE begins when an MHC molecule (*gray*) being manufactured in the cell binds with a peptide (*red*). The resulting complex moves to the surface of the cell, where it is displayed to *T* lymphocytes. The lymphocytes ignore the complex if the peptide is derived from the host's own proteins but lock onto it if the peptide is foreign. This binding activates the lymphocyte.

a gamma value greater than one. Alternatively, the substitutions may confer a disadvantage, causing "negative selection" that lowers gamma to values less than one. Hence, the gamma parameter should reveal the presence of selection.

Hughes and Nei divided the MHC gene into two parts: one coding for the amino acids involved in the binding of the peptides (the peptide binding region, or PBR) and the other comprising the rest of the gene (non-PBR). They then discovered that in the functional MHC genes the gamma values for the PBR segment were greater than one, whereas those for the non-PBR part were less than one. They concluded that selection favors amino acid replacements in the PBR (where most of the MHC polymorphism is indeed concentrated) and disfavors them in the rest of the gene.

In 1991 Adrian V. S. Hill and his colleagues at the University of Oxford presented tentative direct evidence for positive selection of MHC genes by demonstrating that certain human MHC alleles contribute to protection from *Plasmodium falciparum*, the parasite responsible for severe malaria. The PBR of the MHC molecule is thus under selective pressure to diversify, presumably in order to provide protection against the great variety of parasites to which a vertebrate host is exposed. Selection is responsible for maintaining MHC allelic lineages in the population for long periods, enabling the alleles to pass from parent to daughter species.

Because the evolution of MHC diversity depends on the number of breeding individuals, one must assume a certain population size to make statements about the persistence of alleles. In reality, however, we do not know how large the human population was in the past, particularly at the time when the human species emerged.



COALESCENCE MODEL traces gene lineages (*colored lines*) to a common ancestor. This diagram represents a population of five individuals, each with two genes (*circles*). In the absence of selection, the estimated number of generations (*rows*) separating a pair of related genes would equal 10, or twice the effective population size. But because this population is so small, random effects are large, as is the variability of the estimate.

As we mentioned at the outset, small founding populations are frequently postulated for the inception of a species, and indeed such a scenario may well explain the origin of island species [see "Natural Selection and Darwin's Finches," by Peter R. Grant; SCIENTIFIC AMERICAN, October 1991]. But in general, there is no direct information on the size of founding populations. Fortunately, however, MHC polymorphism offers an opportunity to study speciation indirectly: if the number of MHC alleles a daughter species has inherited from the parental species were known (and also the mutation rate and the intensity of selection), the size of the founding population could be estimated.

Let us assume that we have found a certain number of MHC alleles in a population of a given size. If we could follow the genealogy of the alleles backward in time, we would observe first two alleles coalescing, then the next two and so on, until all alleles now present coalesced in a single common ancestor. Imagine that one coalescence has just occurred and we are waiting for the next. The waiting time then becomes a random variable that, theoretically, can have any value from zero to infinity. In reality, however, certain waiting times are likelier than others, and their probability can be calculated from the population size and the number of ancestral alleles—the larger the number of alleles, the quicker the coalescence. Conversely, if we know the coalescence time and the number of ancestral alleles, we can estimate the effective population size.

To obtain values of coalescence time, one compares the nucleotide sequences of the MHC alleles at a given locus, calculates genetic distances between them and represents these differences as a family tree. Yoko Satta of the Max Planck Institute in Tübingen showed how such a tree might be related to absolute chronology by demonstrating that synonymous substitutions in MHC alleles occur with clocklike regularity when viewed over long periods. She was able to calibrate the clock by reference to the fossil record.

The rate she calculated allows one to read off the coalescence times of individual allelic pairs on a family tree, as well as the number of ancestral alleles that existed at any given time in the past. From the known number of extant alleles of MHC-DRB1, we estimate that the long-term effective human population size in the past 0.5 million years has been on the order of 100,000 individuals. Calculations carried out for other human MHC loci generally give similar estimates. The large size of populations is also indicated for other primate species whose MHC polymorphism is reasonably well defined.

These calculations, however, do not exclude the possibility that the population may occasionally have crashed, perhaps after epidemics or famine. Such demographic cataclysms would have produced genetic bottlenecks, so called because they allow only a fraction of

the alleles to make it through into the next phase of the population's evolutionary history. Yet one need not invoke disaster. It is easy to imagine that a small group of individuals might sometimes separate from the main population, migrate to a distant region and then expand in a new environment, giving rise to a new species.

The behavior of genes in the bottleneck phase is difficult to analyze mathematically because of the strong effect of random fluctuations, but it can be simulated on a computer. The computer begins with 100,000 "individuals" bearing 200,000 "genes," each gene carrying one of 40 different "alleles," which occur with equal frequency. The computer draws at random 1,000 genes (and thus 500 individuals), thereby establishing the first bottleneck "generation." From this set, it draws a further 1,000 genes (the second generation), each time replacing the drawn gene with another of the same kind before drawing the next one. After computing 10 generations, the machine counts the remaining alleles and their frequencies. The entire simulation is then repeated a number of times to produce an estimate of the likelihood that all alleles would make it through the bottleneck.

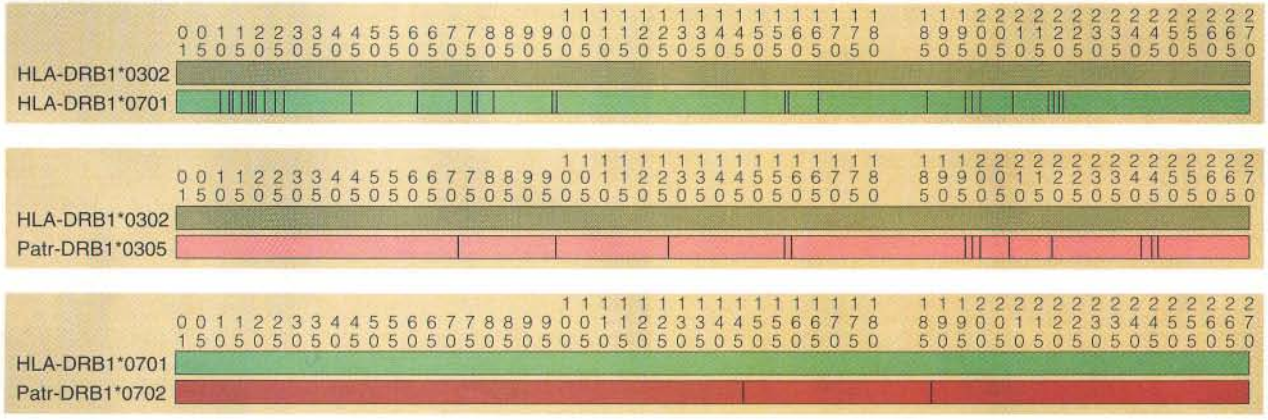
It turns out that all 40 alleles pass through the bottleneck in 60 percent of the simulations. If the bottleneck is much narrower or if it spans many more generations, the probability drops so low that one cannot realistically expect the polymorphism to pass from species to species. We conclude from such simulations, therefore, that the founding population of a species cannot consist of fewer than 500 breeding individuals. In reality, the minimum size is probably much larger because we deliberately set up the conditions of the simulation to result in an underestimate (we considered alleles at one locus only and only those differing at the PBR).

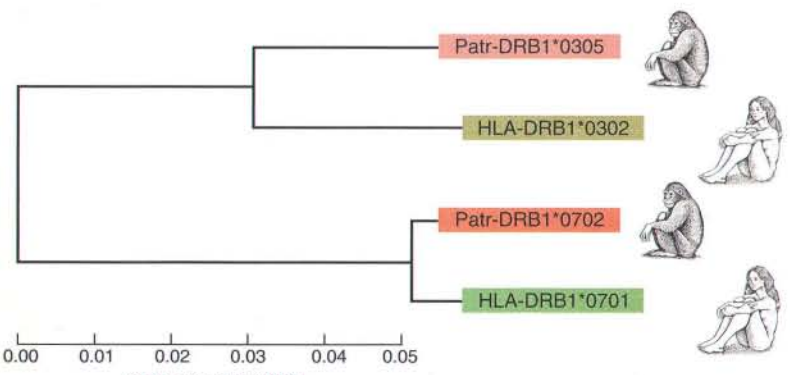
These estimates contradict the popular notion that species arise from small founding populations in which random fluctuations in gene frequencies provide conditions for greater effects of natural selection. MHC polymorphism categorically rules out the possibility that modern human populations are derived from a single individual—an Eve.

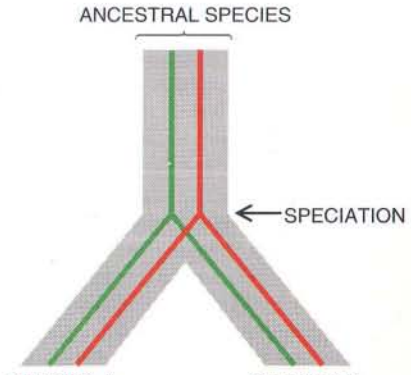
In 1987 Rebecca L. Cann, then at the University of California at Berkeley, and her co-workers reported the results of their analysis of mitochondrial DNA from several human populations [see "The Recent African Genesis of Humans," by Allan C. Wilson and Rebecca L. Cann; SCIENTIFIC AMERICAN, April 1992]. The analysis was neither the first nor the last of its kind, but it received extensive publicity, mainly because of the authors' phrase "mitochondrial Eve," widely interpreted, particularly by the popular press, to mean that modern humans had originated from a single

Trees inside Trees

Transspecies polymorphism is apparent in this comparison of the MHC-DRB1 locus in humans (HLA) and chimpanzees (Patr). In each species, two alleles have been compared; the human alleles have significantly more sequence differences (*vertical lines, top*) than either one has with its counterpart in the chimpanzee. When these differences are converted into genetic distances and represented by an algorithm in a family tree (*bottom left*), the branching pattern implies that the alleles diverged long before the species did (*bottom right*).

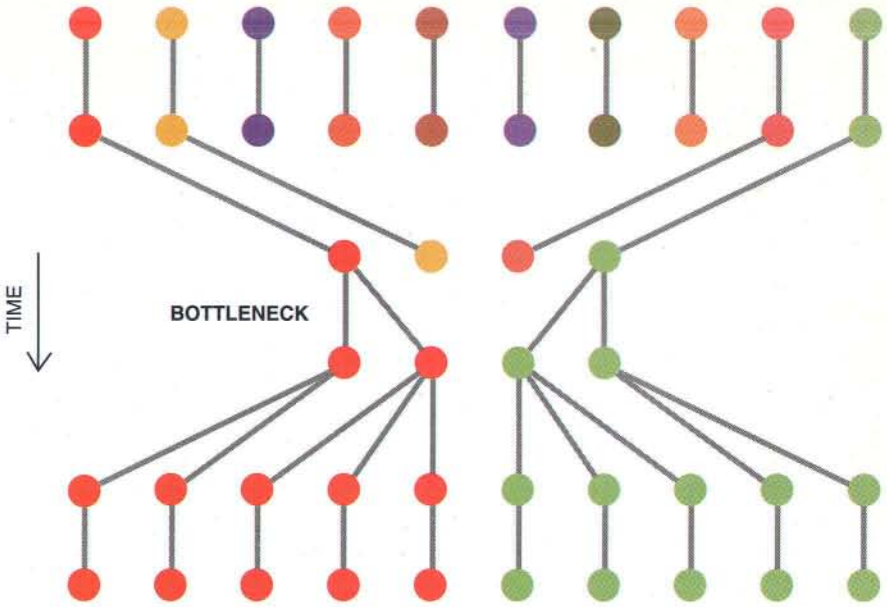






individual. In fact, the study demonstrated no such thing. What the authors did claim to have established—although this, too, is contested by several investigators—is that all mitochondrial DNA variants now present in the human population are derived from an ancestral molecule borne by a female who lived some 200,000 years ago.

This conclusion, even if true, would not mean that the human pedigree began with a single mother 200,000 years ago. It would mean only that the extant mitochondrial DNA "alleles" coalesce to a single ancestral molecule extant at that time. But because mitochondrial DNA is inherited as a unit, it can be regarded as just one of some 40,000 human genes, each of which can, theoretically, be traced back to its own ancestral gene. These genes existed at different times in the past. The MHC genes, as we have seen, can derive from ancestors that existed more than 65 million years ago. The phrase "mitochondrial Eve" led many people to think in terms of pedigrees of individuals rather than pedigrees of genes. The actual data of Cann and her colleagues do not contradict the MHC data, nor do they demonstrate a bottleneck phase in the evolution of the human species.



FOUNDER EFFECT, suggested as a primary cause for the origin of species, should leave a telltale mark in the form of reduced polymorphism. The simplified population shown above is reduced to a "bottleneck" of two individuals, with four alleles at a single locus. These two founders can pass no more than four alleles to subsequent generations and hence to any new species to which they may give rise. In this case, genetic drift during the "bottleneck" phase has left only two alleles to be passed on to the new species. Circles represent genes; colors represent alleles.

The MHC data imply that the early hominid line split, at some stage, into at least two populations—one of which led to modern *H. sapiens.* The population that evolved into *H. sapiens* consisted of at least 500 but more likely 10,000 breeding individuals, who carried most of the MHC alleles and allelic lineages now found in the human population. Although this large ancestral population may have divided into smaller groups, these groups communicated with one another, exchanging genes continuously, thus guarding the great treasure trove of MHC polymorphism from loss by random fluctuation in gene frequencies. The polymorphism that now shields humans from parasites is a heritage that has been handed down through innumerable generations over 65 million years.

Estimating the size of the population that founded *H. sapiens* is only one example of the applications of MHC polymorphism. In the future, it should also be possible to estimate the size of the colonizing tribes in human migration, such as those entering the Americas, Australia, Polynesia and Japan. In more general terms, MHC polymorphism will undoubtedly be exploited to make inferences about the nature of the speciation process itself. It should be possible, for instance, to investigate whether most evolutionary change occurs in small bursts at the time of speciation, as argued by the proponents of the theory of punctuated equilibrium, or whether change continues to occur throughout the life of a species [see "The Evolution of Darwinism," by G. Ledyard Stebbins and Francisco J. Ayala; SCIENTIFIC AMERICAN, July 1985]. It should also be possible to ascertain whether species arise as "buds" from an ancestral species that continues to exist or whether each speciation involves the gradual transformation of one species into another.

The MHC polymorphism will help solve these and other problems in those organisms in which it is present, but the same methods can be extended to other genetic polymorphisms. The genetic systems governing self-incompatibility in plants are a striking example. In many plants, pollen deposited on a stigma fails to germinate and grow into the style of the pistil if the pollen and the pistil express the same allele at a self-incompatibility locus. Several scores of alleles may occur at such a locus.

Thomas R. Ioerger, now at the University of Illinois, and Andrew G. Clark and Teh-Hui Kao of Pennsylvania State University have studied nucleotide sequences of alleles from three species of the family Solanaceae: an ornamental tobacco plant, a wild petunia and a wild potato. They found that some alleles in a given species are more divergent from one another than they are, individually, from their counterparts in another species. They concluded that some allelic lineages predated the divergence of the three species some 27 to 36 million years ago. Hence, in these species as well, the founding populations must have been large.

This finding, so similar to that which links the MHC alleles of humans and chimpanzees to a common ancestor, demonstrates the profound possibilities inherent in the comparative study of allelic diversity. All these investigations, by furnishing an opportunity to study populations that existed millions of years ago, should serve as the basis for a new field: population paleogenetics.

FURTHER READING

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NATURAL HISTORY OF THE MAJOR HISTOCOMPATIBILITY COMPLEX. Jan Klein. John Wiley & Sons, 1986.

A SIMPLE GENEALOGICAL STRUCTURE OF STRONGLY BALANCED ALLELIC LINES AND TRANS-SPECIES EVOLUTION OF POLYMORPHISM. Naoyuki Takahata in *Proceedings of the National Academy of Sciences,* Vol. 87, No. 7, pages 2419–2423; April 1990.

Africanized Bees in the U.S.

Africanized honeybees have reached the U.S. from points south. As more of them arrive, they will certainly wreak some havoc but perhaps not the type their "killer bee" nickname would imply

by Thomas E. Rinderer, Benjamin P. Oldroyd and Walter S. Sheppard

The long-anticipated announcement came in October 1990. Africanized honeybees, more popularly known as killer bees (because of sensationalized accounts of their attacks on people and animals), had finally crossed the Mexican border into the U.S. Less than 35 years after members of a honeybee subspecies living in Africa (*Apis mellifera scutellata*) were released outside São Paulo, Brazil, their descendants—the Africanized bees—had migrated as far north as southern Texas. Today the bees occupy a range of about 20 million square kilometers, encompassing much of South America and virtually all of Central America. And their spread continues. They reached Arizona in 1993 and are expected to colonize parts of the southern U.S. before being stopped by climatic limits, probably by the year 2000.

Their arrival in the U.S. raises many questions. How will the newcomers affect public health and the beekeeping industry? Why were African bees brought to the Americas in the first place? What allowed their progeny to be so extraordinarily successful? And, most important, can anything be done to minimize the impact of settlement by Africanized bees in the U.S.? We and others have devoted a great deal of study to this last question. That work, particularly research exploring the genetic makeup of the insects heading for the U.S., offers hope that efforts to control mating between Africanized honeybees and honeybees common in North American apiaries can be of considerable value.

One already obvious effect of the bees' arrival is heightened concern for public safety. Africanized bees typically defend their hives much more vigorously than do honeybee strains in North America. North American honeybees descend from rather gentle subspecies of *A. mellifera* that were imported primarily from Europe, when early settlers found that the New World lacked native honeybees. Compared with the European bees, those with markedly African traits become aroused more readily and are more prone to sting any person or animal they perceive is threatening their nest. They may also attack in larger numbers (occasionally by the thousands) and persist in the attack longer (sometimes for hours).

Such behavior has reportedly caused one human death in the U.S. and perhaps 1,000 in the Western Hemisphere, and it is responsible for many more fatalities among domesticated animals. Fortunately, most nonallergic individuals will survive an attack if they can run away and so limit the number of stings they suffer. Almost all individuals killed by Africanized honeybees have died because they could not flee—either because they had fallen and injured themselves or had otherwise become trapped.

Beyond posing a public health problem, the bees also promise to threaten the livelihood of thousands of commercial beekeepers (apiculturists) and farmers. Amateur and professional beekeepers alike keep their hives outdoors. It is therefore possible that European queen bees will mate with Africanized drones (males) and thereby introduce increased levels of defensiveness and other costly and troublesome traits into apiary colonies.

The queen's mating choices account for the characteristics of a colony because it is she who lays the eggs. Early in life, she mates in flight with perhaps 15 drones from other colonies and then never mates again. When bees are needed in a colony, the queen lays eggs into individual cells. Fertilized eggs usually give rise to worker bees—females that carry chromosomes from each of their parents and are responsible for foraging and guarding the nest. (If the larva emerging from a fertilized egg is fed a special diet, however, it can develop into a queen.) Unfertilized eggs give rise to drones; these males bear a single set of chromosomes (from the mother), and they die after mating.

If beekeepers are unable to control the infusion of undesirable traits produced by mating between European queens and Africanized drones, their profits will shrink, partly because measures will have to be adopted to protect workers and the public from excessive stinging. For instance, apiaries might have to relocate to sparsely populated areas, and everyone handling the bees will have to wear sturdy protective gear. Moreover, the bees tend to abandon hives more readily than do European bees; repopulating hives can be expensive.

Beekeepers could also face a reduction in honey production, which now amounts to about 200 million pounds annually (representing roughly $100 million in sales). Much research suggests that under climatic and ecological conditions that foster the abundant produc-

THOMAS E. RINDERER, BENJAMIN P. OLDROYD and WALTER S. SHEPPARD have cooperated on several studies and expeditions. Rinderer is a research geneticist and director of the Honey-Bee Breeding, Genetics & Physiology Laboratory in Baton Rouge, La., a part of the U.S. Department of Agriculture's Agricultural Research Service. Oldroyd was a visiting scientist in that laboratory until recently, when he returned to his home base in Melbourne, Australia. There, he is research geneticist at La Trobe University. Sheppard, a research entomologist at the Agricultural Research Service's Bee Research Laboratory in Beltsville, Md., specializes in the molecular aspects of honeybee population genetics and evolution.

AFRICANIZED HONEYBEES have become alert to the presence of an intruder near their hive, as is evident from the raised stance of the bee at the right. Such bees, which look virtually identical to other honeybees, are descendants of a honeybee subspecies (*Apis mellifera scutellata*) that was introduced into South America from Africa in 1956.

tion of honey by European bees, Africanized bees would be less productive.

Meanwhile beekeepers who rent their colonies to farmers for the pollination of such crops as almonds, blueberries, apples and cucumbers would face additional financial losses. Rentals generate an estimated $40 million in fees every year, much of which goes to migratory beekeepers, who truck thousands of colonies to distant sites. Beyond having to exercise particular care to protect the public, beekeepers who maintained many Africanized bees could be prevented from bringing bees into non-Africanized areas.

Farmers who rely on pollination services for the production of $10 to $20 billion worth of crops could be hurt even more. Their costs would go up because protection of the public would require them to purchase services from a reduced number of beekeepers whose stocks were known to be European; such beekeepers might have to travel greater distances or might have to charge more because of the expense involved in keeping their apiaries under control and in attaining certification of their success.

Today's concerns are an outgrowth of an unfortunate series of events that began in the mid-1950s, after the government of Brazil decided to shore up that nation's beekeeping industry. At the time, European honeybees formed the basis for a strong beekeeping industry in many places, but not in Brazil. Brazil had only a small apiculture industry, partly because European honeybees were poorly suited to the country's tropical climate. Rarely, if ever, did a colony survive in the wild, and only considerable effort enabled beekeepers to sustain colonies throughout the year.

It is now evident that the poor performance by the European bees was related to their misreading of environmental cues for reproduction. Direct and indirect studies of genetics indicate that European bees, like all subspecies of *A. mellifera*, trace their ancestry to an Asian species that evolved the ability to regulate body temperature and survive in a temperate climate. The bees withstood the cold mainly by clustering together in sheltered nests and eating stores of honey they had collected in warmer seasons. Later they expanded their range to include Asia Minor, Europe and Africa, ultimately forming 20 or more subspecies adapted to particular locales.

In the course of evolution the behavior of the various European subspecies apparently became highly linked to seasonal fluctuations in day length. When hours of daylight begin to increase, heralding the imminent appearance of flowers, European honeybee colonies expand the size of their worker populations. By the time the flowers bloom, many workers are available to forage for pollen and nectar. Nectar, which contains a great deal of sugar, is converted to honey—a prime source of energy.

Linkage of the life cycle to day length works well in temperate regions, but in Brazil day length bears little relation to the availability of pollen and nectar. The rainy periods that are required for abundant production of flowers do not necessarily coincide with periods of extended daylight. Consequently, European colonies can be induced to expand

MIGRATION OF AFRICANIZED HONEYBEES from outside São Paulo, Brazil, to the U.S. was accomplished in less than 35 years. (Red lines indicate the farthest points of detection in the years indicated.) The insects reached the southern tip of Texas on October 15, 1990, and were first spotted in Arizona in 1993.

even when food supplies are too scarce to support large populations.

In 1956 the best solution to Brazil's beekeeping woes seemed to be importation of a honeybee variant more accustomed to tropical living. The government therefore authorized Warwick E. Kerr, then at the University of São Paulo at Piracicaba, to bring *A. m. scutellata* from the highlands of eastern and southern Africa for study. Kerr obtained 170 queens, although only 46 from South Africa and one from Tanzania survived the journey from South Africa to a research apiary in Rio Claro. (Rio Claro lies roughly 100 miles from São Paulo.) He chose individuals that had already mated with African drones and were thus ready to lay the eggs needed to create complete colonies.

In 1957, within months after the African colonies were established, a visitor to the experimental apiary removed screens that had been placed at hive entrances to block queens from leaving. The reasons for the removal are unclear, but before the act was discovered, 26 colonies had abandoned their hives with their queens. For years, those liberated colonies were thought to have been the founders of the entire Africanized population. Recently, however, scientists have learned that soon after the initial release, queens reared from the remaining colonies were distributed to beekeepers in Brazil. The additional releases undoubtedly helped to ensure that enough African insects would be available to establish permanent feral populations of Africanized honeybees in Brazil.

The freed bees and their descendants found Brazil to be a hospitable place, and so they thrived. Compared with European bees, the newer arrivals were better able to take their reproductive cues from variations in the availability of rainfall and flowers and were better equipped to cope with dry seasons. When flowers are abundant, Africanized colonies engage in a process known as reproductive swarming: the queen and a good many hive members split off to establish a new, growing colony. This swarm leaves the remainder of the original colony with a young queen, who repopulates the hive. When floral resources dwindle severely, Africanized bees are likely to abscond—they gather any remaining honey and abandon the hive en masse, to try to find a more hospitable locale. (European bees, in contrast, swarm perhaps once a year and rarely abscond.)

As the Africanized bees flourished in Brazil, they fanned out in all directions, including into areas that previously had no beekeeping. In the 1960s they began to draw an increasing amount of attention, especially for their intense nest defense, and it became clear that they could be very troublesome.

By 1972 the U.S. government began considering the potential impact of the bees on the U.S. A committee organized by the National Academy of Sciences and funded by the U.S. Department of Agriculture found some cause for worry. Although bees in southern Brazil were surely prone to stinging, they were manageable. Areas that supported beekeeping before the release of the African bees continued to do so. But bees in the north—those on a trajectory headed for the U.S.—were unacceptably defensive. Not surprisingly, northern Brazil, which had supported little beekeeping previously, still had little. Consistent with the northern findings, later work indicated Africanized bees that had journeyed north into Venezuela and beyond kept a strong propensity for stinging. They also retained their tendency to swarm and abscond frequently.

In the mid- to late 1980s the U.S. government, with the cooperation of Mexico, decided to try retarding the spread of the bees into the U.S. by establishing a "bee-regulated zone." The final plan called for detecting and killing any swarms that arrived in parts of Mexico the bees would have to traverse in order to reach the U.S. Combined with weather inhospitable to migration, that effort (which proved more difficult to implement than had been hoped) may well have delayed the arrival of the bees for a while. But it was clear they were not going to be stopped altogether.

Interestingly, as anxiety mounted in the U.S., Brazilians found a way to use Africanized bees for the intended purpose: to strengthen their beekeeping industry. Initially many beekeepers abandoned the craft. But the Brazilian government embarked on a campaign to teach potential beekeepers how to cope and to instruct the public about how to

avoid the bees and handle attacks. Now a new generation of apiculturists has emerged. Indeed, in some parts of Brazil that were once unable to sustain European honeybees, people earn their livelihood through keeping Africanized bees and harvesting their honey. These individuals maintain reasonable traits in their stocks by destroying queens in the most defensive and least productive colonies.

Unlike Brazil of the 1950s, the U.S. has little to gain from settlement by Africanized bees. And so the bees' entry into Texas and Arizona has added new urgency to the question of whether the introduction of African traits in apiaries and in the wild can be minimized. In theory, two major strategies might be helpful. Certainly, beekeepers could protect their stocks to some extent by practicing "requeening" frequently. The procedure involves inducing colonies to accept substitute queens of a beekeeper's choosing, often purchased from breeders of queens. Beekeepers can thereby ensure that their queens are European and (if so desired) that they have already mated with European drones. Many apiculturists are already adept at requeening. They use it to increase the production of offspring (replacing old, less productive queens with new ones) or to control the genetic makeup, and hence the characteristics, of hive populations.

Another protective strategy, known as drone flooding, calls for maintaining large numbers of European drones in areas where commercially reared queen bees are mated. Even if the areas have been invaded by Africanized émigrés, the vast number of European males would ensure that European queens would mate almost entirely with European drones.

Furthermore, the presence of many European bees would increase the probability that Africanized queens, too, would mate primarily with European drones. If the queens of successive generations then continued to mate with European drones, the gene pool of the bee populations in the affected areas would consist mostly of European DNA. Then the bees would have predominantly European traits. In the end, such gentle hybrids might actually prove to be quite valuable. Some scientists have reported that Africanized bees may be more resistant to acquiring parasites and disease. If these advantages could be harnessed by breeding programs, they might help bees in North America fight off a growing invasion of mites.

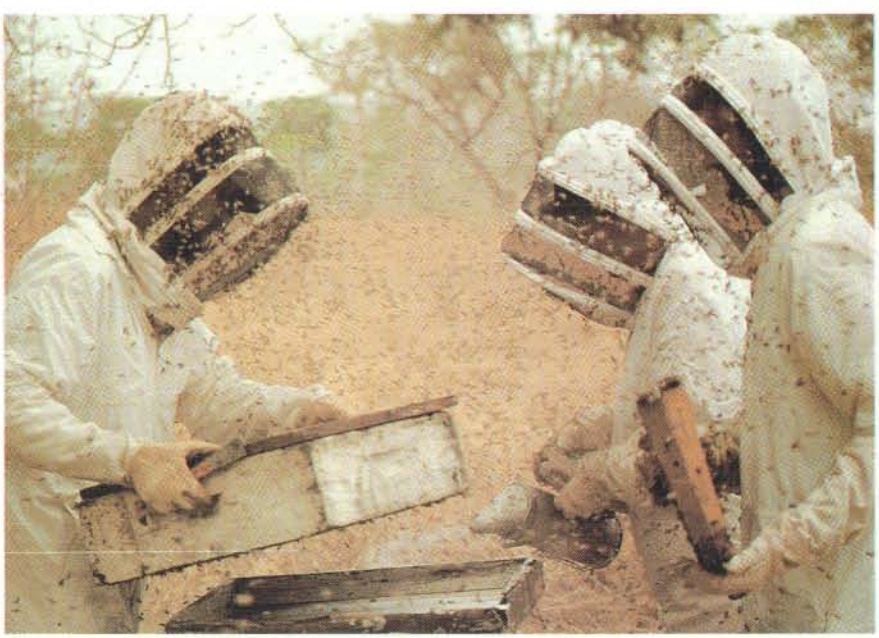
Of course, the drone-flooding strategy assumes that honeybees bearing essentially African genes and those bearing essentially European genes can hybridize—that is, mate with each other and produce viable offspring bearing genes and traits from both parents. But can the two groups in fact hybridize? For many years, researchers were unsure of the answer. Some early studies in the 1980s that examined morphology, or physical features, of bees in areas known to have been invaded by the descendants of *A. m. scutellata* seemed to indicate that hybridization was indeed occurring, as did studies of enzymes. But other work disagreed.

Morphological comparisons are much more difficult than they might sound. Even if one examines the extremes—African bees living in Africa and European bees living in Europe—the two groups look alike. But colonies can be distinguished by a statistical procedure called multivariate discriminant analysis. In doing such an analysis, researchers measure many different body parts—among them, the length and width of the wings and leg segments, and the angles at which various veins intersect in the wings. Although the mean scores for African and European samples will not differ significantly on any one measure, combining group means for many measures makes it possible to distinguish overall differences that do exist.

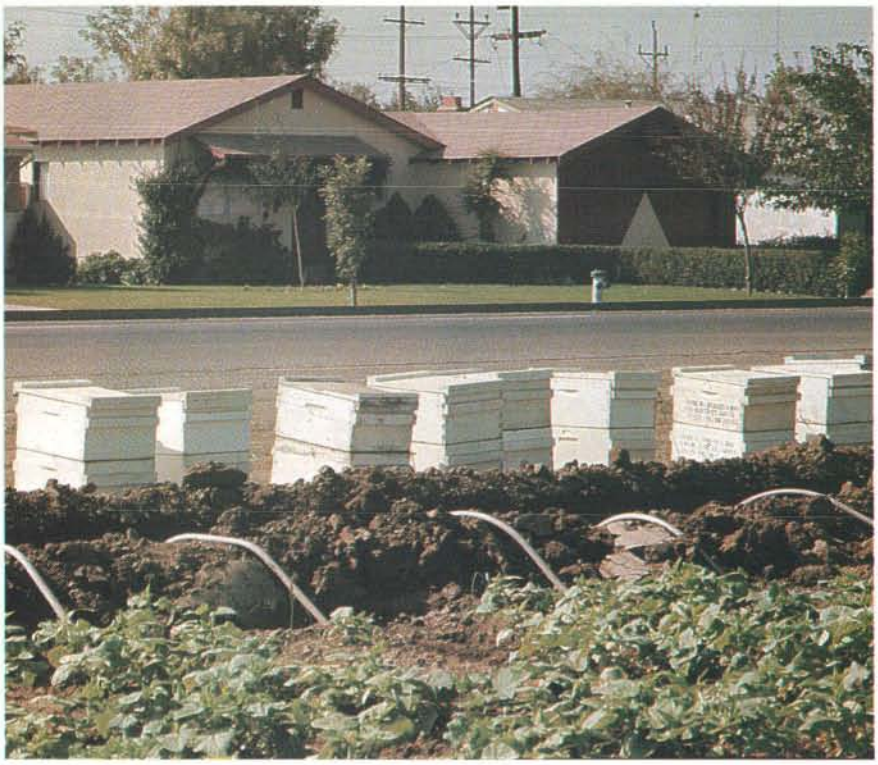
To assess whether the invading bees in Central and South America differed physically from *A. m. scutellata*—which would suggest genetic mixing had taken place—we compared their final scores with those attained for African and European bees. The comparison revealed that feral populations in Mexico, Brazil, Argentina and Venezuela resembled both European and African bees to various degrees, although they were more like the African bees.

Similarly, when we plotted summed measures for three different clusters of traits against one another on three axes, the point representing purely African bees fell far from that representing purely European bees in North America [*see bottom illustration on next page*]. The points representing bees from Mexico, Brazil, Argentina and Venezuela fell in between, roughly a third of the way between those two extremes but closer to the African value. These findings suggested that the populations advancing toward the U.S. were not pure Old World African stock; they were indeed hybrids that had acquired some European genes in their travels.

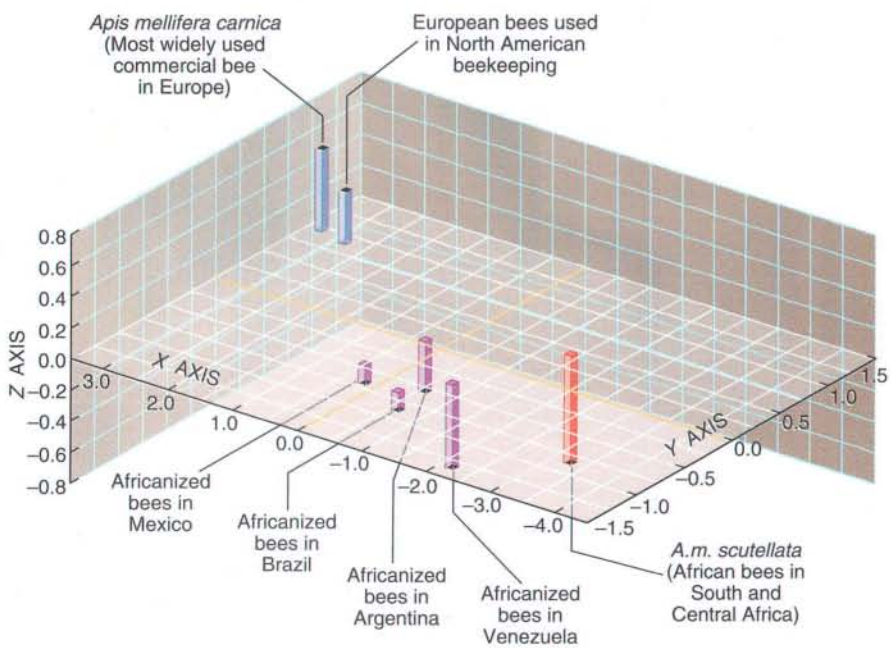
Other conceivable explanations for the morphological findings existed, though. One was that a founder effect was responsible. Perhaps the relatively few African bees that were originally imported to Brazil happened to carry genes that caused them to look European. In that case, their progeny in the Americas would also physically resemble European bees even in the absence of hybridization. Alternatively, natural selec-



PROTECTIVE CLOTHING is essential for anyone who works around hives of Africanized bees. Compared with the relatively gentle strains of honeybees common in the U.S. (originally imported from Europe), the Africanized bees are more easily aroused. Entire populations of hives can come pouring out in a flash, ready to pursue doggedly and sting any perceived intruder.



MELON PLANTS (*foreground*) are growing close to a residential area in northern California. They are about to be pollinated by European honeybees stowed in nearby boxes. As Africanized bees settle in the U.S., farmers may have more difficulty finding European bees to rent for pollination and may have to pay more for those that are available. For that reason and others, the incursion of Africanized bees into the U.S. could shrink annual profits of beekeepers and farmers.



MEASUREMENTS OF PHYSICAL FEATURES in European, African and Africanized honeybees have been summarized on this three-dimensional plot. The axes represent the collected measures for distinct clusters of traits. One base of each cylinder sits on the floor formed by the *x* and *y* axes. The opposite end of the cylinder (*shaded black*), lying above or below the floor, marks the intersection of *x*, *y* and *z* coordinates; that base represents the overall morphology of the group. The morphology of the Africanized bees (*purple*) is between that of the European (*blue*) and African (*red*) bees—which suggests that the Africanized bees are by-products of mating between European and African bees in the Americas.

tion in the Americas may have favored the survival of African bees that by chance had European-like physical traits.

The attractiveness of these explanations dimmed, however, when the data from multivariate analyses were combined with results from studies that compared enzymes in African and European bees. Jorge A. Lobo and his colleagues at the University of São Paulo at Ribeirão Prêto knew that 98 percent of African bees carry one form, or allele, of a gene specifying the amino acid composition of a particular enzyme: malic acid dehydrogenase. They also knew that this same allele—and therefore the isozyme, or enzyme variant, it encodes—is much rarer in European bees.

When the group surveyed the forms of malic acid dehydrogenase in the bees of Brazil, they deduced that only 70 to 80 percent of the insects harbored the allele common in African bees. Studies of other isozymes yielded a similar pattern. These results led Lobo's group to conclude that at least some Africanized bees are the products of hybridization. It is highly doubtful that both the morphological and the isozyme differences between Africanized and Old World African bees could be the result of happenstance.

Yet the findings favoring hybridization were contradicted by other observations. Notably, bees in the colonized areas seemed to display clearly African traits, namely, intense defensiveness and frequent swarming and absconding. If hybridization was going on, it certainly was not obvious behaviorally. The first direct genetic studies raised similar doubts. They compared mitochondrial DNA in bees from colonized areas with that in European and African bees. Mitochondria, the energy factories of cells, contain small rings of DNA that are distinct from the chromosomal DNA housed in the nucleus. Nuclear DNA directs the emergence of physical and behavioral traits. Mitochondrial DNA provides about a dozen genes required strictly for energy production. Most animal species (including humans) inherit their mitochondria, and thus mitochondrial DNA, exclusively from the mother.

It turns out that African and European bees differ slightly in the sequence of nucleotides (the building blocks of DNA) in their mitochondrial DNA. Hence, by identifying known markers of the variable DNA segments from bees in Africanized areas, investigators were able to trace the maternal lineage of the insects to either Africa or Europe. (The markers used are DNA fragments that form

when mitochondrial DNA is cleaved by a restriction enzyme. For example, one fragment generated from African DNA appears as two smaller fragments in European DNA.)

The first published reports found European mitochondrial DNA to be virtually nonexistent in the bees studied. This absence implied that almost none of the sampled bees had descended from European queens. If hybridization had taken place, one would expect to see a greater representation of European mitochondrial DNA.

The results seemed consistent with the possibility that something was preventing hybridization from taking place. Yet it was also possible that the bees in the studies came from tracts that previously supported few feral European bees. In that case, there would be little hybridization because almost no European bees would have been available to interact with incoming African bees.

Determining whether hybridization could in fact occur required investigation of bee colonies from areas known to have been supporting European honeybees when the newcomers arrived. We therefore traveled to Argentina, which lies west of the thin, southernmost part of Brazil and extends much farther south, into a temperate zone. Africanized bees have not become established in the southern half of the country, which supports abundant beekeeping with European strains. But they have established large populations in the northern half, particularly in the topmost quarter of the country, which has never maintained as many European bees.

Julio A. Mazzoli, a graduate student from the University of Buenos Aires, helped us find more than 100 colonies in bridges, trees, electric utility poles, fruit boxes and other enclosed areas favored by honeybees. The collection included representatives from areas extending from the north into the south [*see illustration on this page*]. Back in our laboratories, we evaluated the morphology and the composition of mitochondrial DNA. Our collective results showed decisively that hybridization had taken place. As part of our evidence, we found that a large number of the sampled colonies had physical features intermediate between those of European and African bees. Further, more than a quarter of the colonies either displayed African morphology (reflecting the activity of nuclear genes derived from African ancestors) yet bore European mitochondrial DNA (reflecting the influence of a female European ancestor) or else displayed European morphology yet bore African mitochondrial DNA.

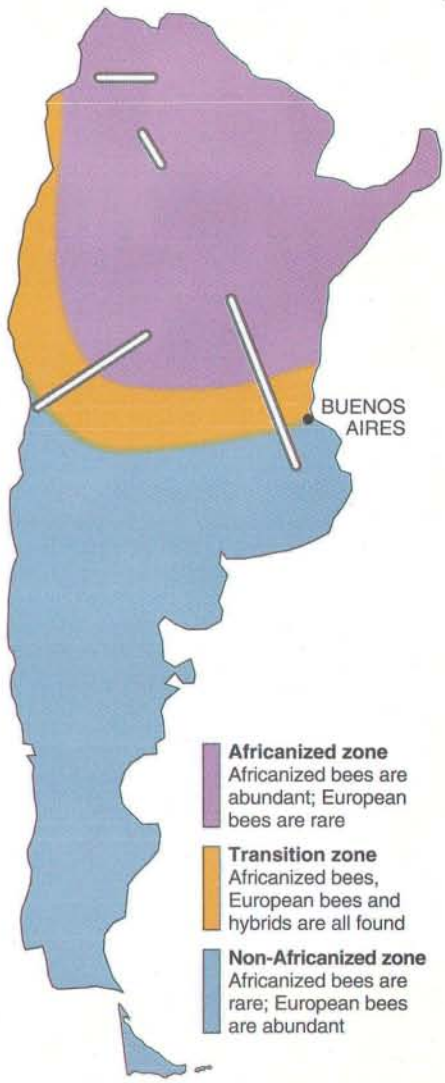
The morphological work yielded another interesting finding: European physical features were more prominent in the southern, temperate regions of the studied territories than in the northern corner, where African morphology predominated. But in a band of fairly temperate territory between those areas, no single cluster of morphological features predominated. This mixture of traits implied that hybridization had occurred extensively in the intervening zone, a conclusion supported by isozyme studies. We found relatively few hybrids outside the transition zone presumably because conditions in the tropical north favor survival of bees having primarily African traits, whereas conditions in the temperate south favor survival of bees having primarily European traits.

Such selective pressures may lead to a similar pattern in the U.S., where the southernmost regions have a subtropical climate and northern areas are temperate. European-like bees may be less competitive in the Deep South, and African-like bees should be less competitive in the North. In the intervening central regions, there may be a mixture of hybrids whose gentleness and tolerance of cold increase with increasing latitude. It is also possible that hybrids will be abundant in some central areas during the warm seasons but will disappear in the winter.

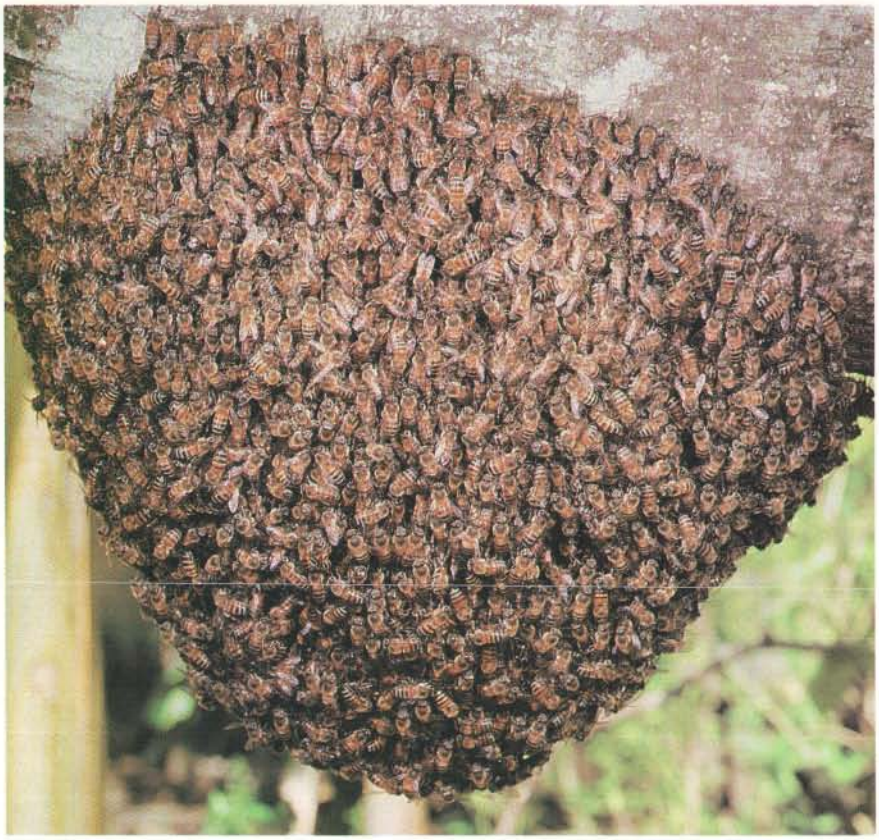
Because there were few European bees in the tropical regions of Argentina, we could not determine whether the presence of a sufficiently large European population would cause African-like bees to mate with them and produce hybrids that survived and reproduced well in the tropics. We knew only that such behavior was commonplace in temperate areas. If hybridization does not occur readily in the tropics, then the strategy of flooding commercial breeding areas with European bees might prove ineffective in parts of Florida, Texas and other subtropical regions of the U.S.

We sought an answer in the Yucatán Peninsula of Mexico. The peninsula has an ideal combination of a tropical environment and an extensive, long-established population of European honeybees. In fact, the Yucatán has the greatest concentration of commercial honeybee colonies in the world. This was the first massive population of European bees encountered by the expanding populations of Africanized bees as they migrated north from Brazil.

We again collected samples from a large tract. This time we relied on the cooperation of beekeepers, who own most of the bees in the Yucatán. Despite being cared for by humans, the honeybees in the Yucatán are probably the genetic equal of feral bees. Beekeepers obtain them by putting out boxes the insects can colonize. Owners usually make little effort to control the genetic makeup of the hive, other than killing older (less productive) queens and allowing hive members to raise a replacement. An occasional beekeeper will, however, practice requeening with pre-mated European queens.



ARGENTINA can be divided into three zones based on the abundance of Africanized bees. In much of the north (*purple*) the bees are present year-round. In most of the south (*blue*), they are absent. Recent analyses of morphology and mitochondrial DNA in bees from tracts crossing all three areas (*white bars*) indicate that Africanized bees, European bees and a range of hybrids coexist in the intervening transition zone. This finding has helped confirm that mating between Africanized and European bees can yield viable offspring.



CLUSTER OF AFRICANIZED BEES hangs from a tree limb, the insects' temporary home until they can construct a hive in some protected place. Such bees swarm—leave their original hive to establish a new one—as part of the processes by which bee colonies reproduce. Frequent swarming by Africanized bees has contributed to their rapid spread through much of the Americas.

All but a few of our samples came from colonies that had not undergone requeening in the two years since Africanized bees had first been detected on the peninsula. Most of the insects still possessed clearly European morphology, but some possessed mainly African morphology, and many had intermediate morphologies indicative of hybridization. Mitochondrial analyses provided still more evidence of interbreeding: a number of colonies displayed either European morphology and African mitochondrial DNA, or the reverse. Thus, a tropical environment does not appear to pose an unbreachable barrier to hybridization.

The least evidence of African traits appeared in the few colonies that had been requeened. This simple observation implies that requeening—one of the chief tools beekeepers have for controlling the Africanization of their stocks—can certainly be helpful.

Our conclusion that significant hybridization can be achieved in tropical areas has recently been confirmed by Robin F. Moritz of the Technical University of Berlin and Michael S. Meusel of the Bavarian Agricultural Institute for Apiculture in Erlangen, Germany. In a survey of feral Africanized honeybees in Brazil, they found that 17 percent of the colonies had European mitochondrial DNA. The team also mathematically modeled the effects of intensive reproductive swarming by Africanized bees on the composition of bee populations in areas that originally supported only European honeybees. The results show that rapid growth of Africanized bees, combined with the survival advantage they enjoy in tropical environments, could enable Africanized bees to predominate over hybrid or other bees with European traits. So it seems that efforts to foster hybridization in the subtropical areas of the U.S. might require continuous requeening with European bees.

Nevertheless, the potential of Africanized honeybees to hybridize successfully with European honeybees is good news for beekeeping. We anticipate that frequent requeening of commercial colonies and drone flooding in commercial queen-breeding areas would serve to dampen the acquisition of unwanted African traits. We should note, though, that there are dissenters who contend that hybridization efforts will fail to prevent the eventual widespread introduction of dramatic African traits into honeybee populations. These observers hold that Africanized bees will inevitably come to dominate in regions that initially show signs of hybridization. Our evidence does not support that view. We found an abundance of hybrid bees in the transitional zone of Argentina some 20 years after Africanized bees had arrived there.

If we are correct that Africanization of U.S. apiaries can be limited, then it seems that, with care, the practice of transporting bees to crops could be continued safely without leading to the significant establishment of Africanized bee colonies in new territories. Fortunately, there are ways to assess the character of individual colonies, and these methods could be employed to guarantee that colonies moved from place to place are European.

It is inevitable that the incursion of Africanized bees into the U.S. will increase the costs of managing commercial colonies, at least temporarily. It is also likely that some African genes will spread through feral and managed bee colonies. Yet vigilance and coordination by apiculturists have every chance of preserving the European behavior of commercial honeybee stocks, thereby reducing the damaging effects of Africanized insects on beekeeping and allaying the fears of the public.

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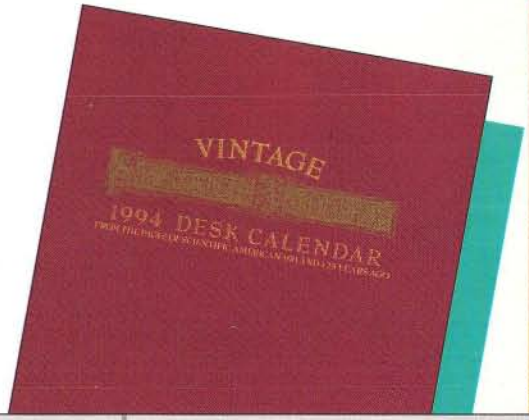

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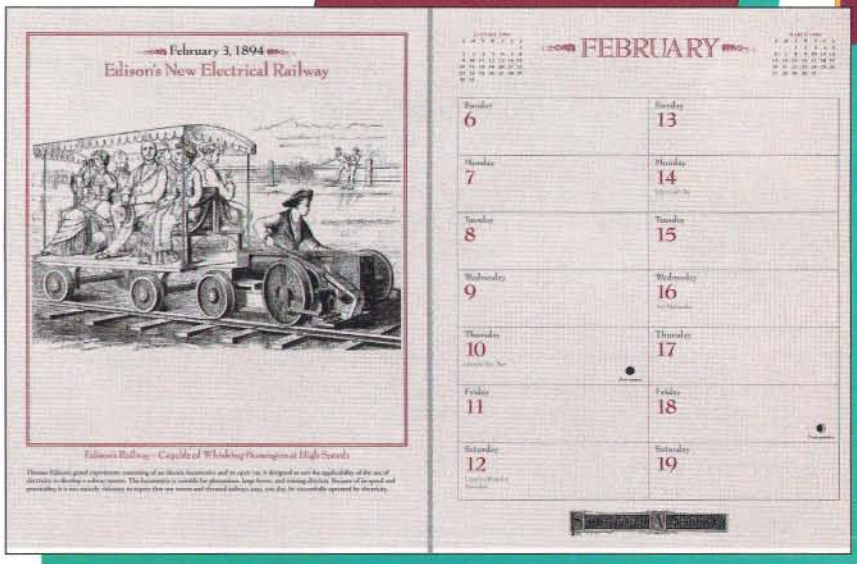

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Drugs by Design

Structure-based design, an innovative approach to developing drugs, has recently spawned many promising therapeutic agents, including several now in human trials for treating AIDS, cancer and other diseases

by Charles E. Bugg, William M. Carson and John A. Montgomery

Most drugs on the market today were found either by chance observation or by systematic screening of large numbers of natural and synthetic substances. In many cases, trial-and-error refinement of substances uncovered by the first two means later led to increased potency or decreased toxicity. Those traditional methods of drug discovery are now being supplemented by a more direct approach, made possible in part by improved understanding of the molecular interactions that underlie diseases.

More and more investigators, including us, are beginning to derive fruitful results from what is called structure-based drug design. Our starting point is not the drug, but its molecular target in the body. We solve the three-dimensional structure of a substance known to participate in some disorder. Then we build a chemical that precisely fits the target and alters its activity. For instance, we might design a compound to block the catalytic site of an enzyme essential to viral replication. We would thereby prevent the virus from reproducing and so would halt the spread of infection.

By somewhat simplistic analogy, standard tactics of drug discovery are akin to making and testing many keys in order to find one that happens to fit a lock of unknown shape. In contrast, prior study of the shape and arrangement of tumblers in a lock would lead to rapid design of an effective key.

In spite of the relative inefficiency of the traditional approaches, they have provided treatments for everything from minor aches to life-threatening illnesses. Today they also benefit from automation, which has markedly speeded up large-scale screening efforts. Yet structure-based methodology can yield promising drugs more quickly and less expensively. Indeed, because the final products are custom-tailored to their targets, they tend to be more potent, more specific and less toxic than remedies discovered in other ways.

Our experience in creating a set of potential drugs—one of which is now in human trials for psoriasis and a form of *T* cell lymphoma—illustrates the process and the power of structure-based design. Ours is by no means the only product of structure-based technology to have reached an advanced stage of development, however. Another, called captopril, is already widely used for the treatment of hypertension. Several others, produced by various laboratories, are being evaluated in humans for therapy of a host of disorders, including cancer, AIDS, glaucoma and the common cold. A number of additional compounds are in less advanced stages of investigation. Although not every drug that reaches late stages of testing proves useful for therapy, the products that are now in or are moving toward clinical trials are quite impressive.

The scientific concepts underlying all this activity were understood 50 years ago, but their practical application lay beyond the reach of the existing technology. Paul Ehrlich, the German bacteriologist, had long since demonstrated that drugs often induce physiological effects by binding to target structures (receptors) that participate in normal cellular activities. Investigators appreciated as well that the shape of a drug and its chemical composition had to complement that of the binding site on its receptor—typically a protein. Nevertheless, progress in drug discovery proceeded slowly, by empirical means, until the 1970s.

At that time, new methods became available for obtaining pure samples of many protein targets. Simultaneously, workers improved x-ray crystallography, the one imaging technique then capable of revealing protein structure. In this technique, crystals are bombarded with x-rays. The crystal diffracts the rays, creating a splatter of spots on photographic film or on newer types of electronic detectors. The distribution of atoms within the crystal influences the diffraction patterns that emerge. Hence, with the help of sophisticated computer programs, the patterns can be translated into maps indicating the three-dimensional structure of the protein molecules within the crystal.

Miguel A. Ondetti and David W. Cushman and their colleagues at the Squibb Institute for Medical Research (now Bristol-Myers Squibb) were the first to successfully exploit crystallography for drug development. They did not know the precise architecture of their target: human angiotensin-converting enzyme, a participant in hypertension. But they did know the conformation of a closely related enzyme. Using that information, they came up with captopril in 1975.

Two of us (Montgomery and Bugg)

CUSTOM-MADE DRUG, the multicolored structure at the center, is a highly potent inhibitor of the enzyme purine nucleoside phosphorylase (PNP), represented by blue spheres. The inhibitor, developed using the structure-based drug design method, was created specifically to fit snugly in the enzyme's active site. It is now being tested in animals for the treatment of arthritis, and a closely related compound is in clinical trials as a therapy for psoriasis and for one form of cancer.

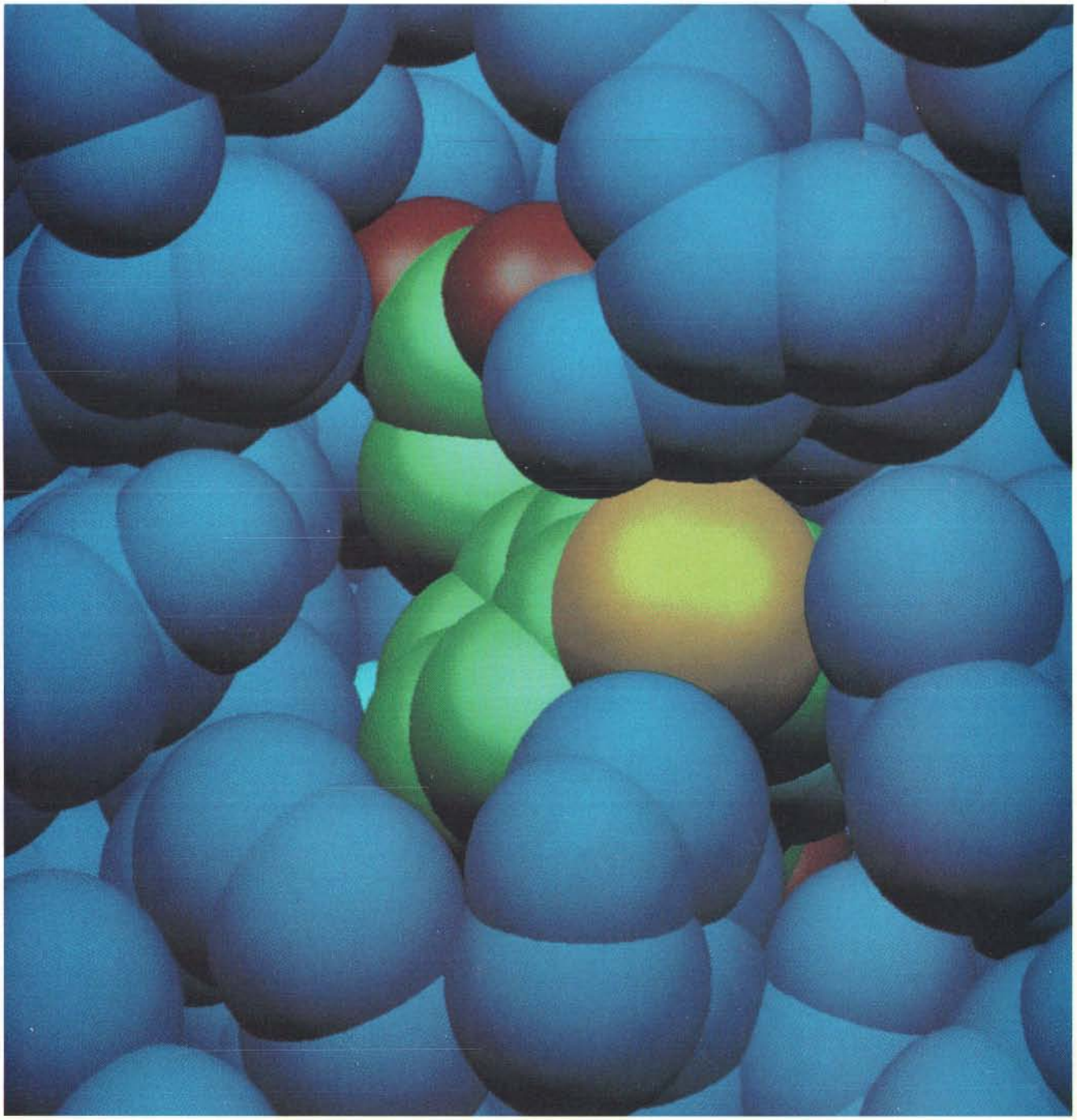
CHARLES E. BUGG, WILLIAM M. CARSON and JOHN A. MONTGOMERY collaborate on drug design in Birmingham, Ala. Bugg is director of the Center for Macromolecular Crystallography, associate director of the Comprehensive Cancer Center and professor of biochemistry at the University of Alabama at Birmingham. Carson is director of the Computer Graphics Core Facility at the Center for Macromolecular Crystallography. Montgomery is executive vice president and director of research at BioCryst, a company devoted to structure-based drug design, and distinguished scientist at the Southern Research Institute.

began to collaborate on drug design in the late 1970s. A decade later our program moved to BioCryst Pharmaceuticals, which Montgomery and Bugg helped to establish. BioCryst is among several young companies devoted to structure-based drug design. The pioneer was Agouron Pharmaceuticals in La Jolla, Calif., formed in 1984.

In the 1970s, as now, enzymes were the favored targets because they control important biochemical processes in diseases. Also, one can impair their activity relatively easily, by fitting small molecules into their active (catalytic) sites. Drugs aimed at other kinds of targets—including nucleic acids (DNA and RNA) and protein receptors for certain hormones—are under study as well. But in many cases, these targets pose greater design challenges. For example, compounds created to regulate the activity of many hormone receptors would have to be more complex than enzyme inhibitors and would have to form more bonds with the receptors.

One of our major objectives was to design a molecule that would inhibit the enzyme purine nucleoside phosphorylase (PNP). PNP normally operates in the "purine salvage pathway" of cells. It takes up individual nucleosides, which consist of a nitrogenous substance known as a purine base (such as guanine) and a sugar. With the help of a phosphate ion, PNP cleaves the purine from the sugar, giving rise to a free purine base and a phosphorylated sugar. Once the purine is released, the cell can destroy it or recycle it to build any of a number of molecules, such as a building block (nucleotide) of DNA.

Unfortunately, PNP can also cleave certain anticancer and antiviral agents that are synthetic mimics of natural purine nucleosides; it can thereby interfere with therapy. One such substance is ddI (2′,3′-dideoxyinosine), which the



Food and Drug Administration approved as a treatment for AIDS in 1991. It was our goal to construct an entity that when administered with the nucleoside mimics would inactivate PNP long enough for the anticancer and antiviral agents to accomplish their therapeutic missions. To serve as a drug, our compound would also have to be able to cross membranes to the interior of cells, where PNP does its work. Other investigators had already identified a few inhibitors of PNP, but none that was potent enough to be useful for therapy and also capable of crossing the cell membrane intact.

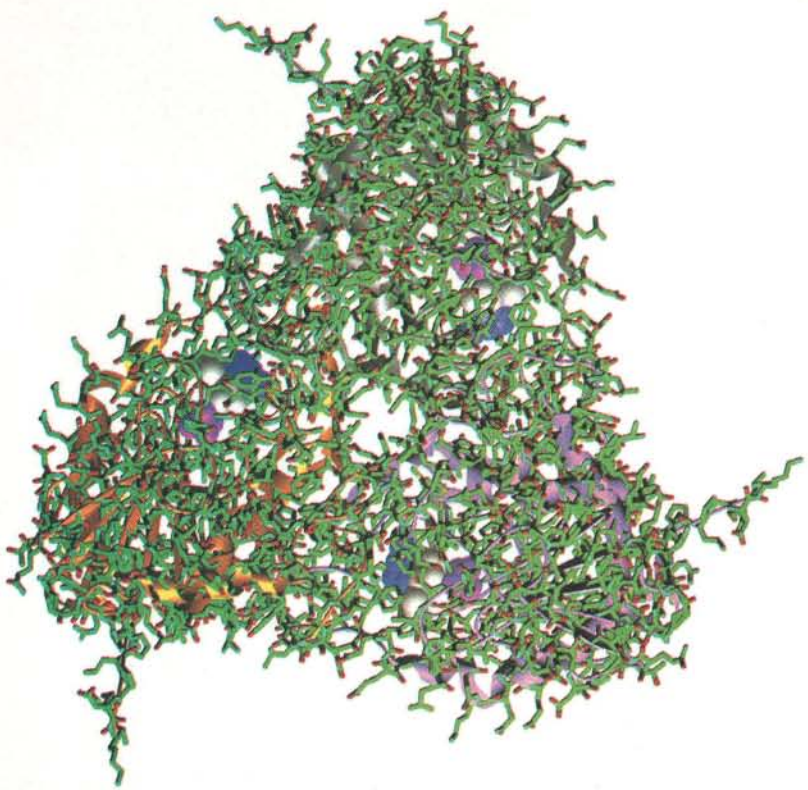
Shortly after we began this project, we gained even more incentive to design powerful PNP inhibitors. Accumulating evidence indicated that the body needs PNP for the proper functioning of *T* cells but not other components of the immune system. We, like other research teams, quickly recognized that inhibitors of PNP might selectively suppress the excessive *T* cell activity associated with an array of autoimmune disorders, such as rheumatoid arthritis, psoriasis, systemic lupus erythematosus, multiple sclerosis and insulin-dependent (juvenile-onset) diabetes.

Having fixed on PNP as our target protein, we followed a systematic strategy for designing inhibitory compounds. In short, we first determined the three-dimensional arrangement of the target's constituent atoms, paying particular attention to the active site. Next we turned to our computers. As we viewed a candidate on a monitor, we worked it into the active site, examining how well the shape and chemical structure of the candidate would complement that of the site. We also used programs to help us estimate the strength of the attractive and repulsive intermolecular forces between a candidate and the active site.

A tight fit is necessary for potency and specificity. A drug that remains bound to its target and inactivates it for a long time can be administered in lower doses than can one that separates from its target rapidly. Further, a substance designed to mesh perfectly with a particular binding site of one protein is unlikely to interact well with any other molecule; therefore, the substance should minimize unwanted interactions and, with them, side effects.

We synthesized only those chemicals that our computer simulations suggested would have greatest affinity for the target. Then we assessed the effects of the drugs on the activity of the target molecule and compared the proposed and the actual fit. Because modeling programs are imperfect, certain compounds we synthesized did not live up to expectations. After exploring the reasons for the successes and the failures, we returned to the computer to propose modifications that might increase the effectiveness of drug candidates.

This iterative strategy—including repeated modeling, synthesis and structural analyses—led us to a handful of highly potent compounds that tested well in whole cells and in animals. Had a compound encountered a difficulty in the cellular or animal tests (such as trouble passing through cell membranes), we would have revisited the computer to correct the deficiency. Then we would have cycled a modified drug through the circuit again.



OVERALL STRUCTURE OF PNP is highlighted in this computer-generated image colored by atom type. The enzyme consists of three identical lobes, or subunits, arrayed around a central axis. The subunits are distinguished by distinctly colored ribbons representing the protein backbone of the subunits. The three active sites are shown filled by a purine nucleoside and a phosphate ion (*structures depicted by large spheres*), the substances normally acted on by PNP.

The entire protocol, from choosing the target to creating a drug suitable for clinical trials, can probably be accomplished today in two or three years. But back in the 1970s the first crucial step, determining the structure of the target, proved to the most laborious of all. It occupied our attention and that of a team of crystallographers led by Steven E. Ealick, then at the University of Alabama at Birmingham, through most of the 1980s.

In our case, the stumbling block did not lie with obtaining pure PNP or converting the protein into crystals. Robert E. Parks, Jr., and Johanna D. Stoeckler of Brown University had already isolated the enzyme from human cells. They supplied quantities to William J. Cook, also at Birmingham, who succeeded in preparing the well-ordered crystals required for x-ray studies.

We were also able to demonstrate easily that crystalline PNP is essentially identical to PNP in the body. If the structure were profoundly different, we would have had no justification for basing drug design on the crystal structure. In addition, Jon M. Crate, then a graduate student in Bugg's laboratory, established that a crystal of the protein was able to function normally. It catalyzed the same reaction that PNP induces in living systems.

The real aggravation arose when we proceeded to the detailed structural determination. In the early years we had to depend on an x-ray source that generated relatively low-intensity waves. The resulting low-resolution diffraction patterns enabled us to discern the overall shape of the molecules, but we could not properly place the individual atoms. We eventually filled in the missing details in collaboration with John R. Helliwell of the Daresbury Laboratory Syn-

chrotron Radiation Source in England. The synchrotron emitted the intense x-rays needed for high-resolution imaging. Today greatly improved equipment and more synchrotron facilities are available for protein crystallography.

The x-ray data established that PNP crystals are highly porous, a feature that proved useful for our understanding of the ability of proposed drugs to inhibit PNP activity. We learned, too, that the functional PNP enzyme exists as a trimer: a unit of three joined monomers (single PNP molecules) [*see illustration on opposite page*]. And we showed that the trimer has three identical active sites, one at each junction between monomers. (Hereafter, we will speak as though there was just one active site, formed by two adjacent monomers.)

Information of perhaps greater import emerged from analyses of the complexes formed when synthetic nucleosides, including previously discovered inhibitors, were attached to the active site. This work showed us the shape of the site, which is essentially an irregular indentation on the surface of the enzyme. These investigations additionally revealed the identity of the exact amino acids constituting the active region; such detail was a prerequisite to drug design.

The structural determinations also yielded a surprise. The shape of the enzyme apparently changes when the active region binds another molecule. In other words, the lock-and-key analogy mentioned earlier has a fallacy: the shape of the lock is not static, but flexible. For instance, a stretch of amino acids in each PNP monomer forms a loop that serves as a swinging gate. It often covers the nearest active site, but it can move to accommodate a nucleoside or some imitator. Awareness of these conformational changes critically aided our modeling efforts because we could predict which parts of the PNP structure could change shape to interact with a proposed inhibitor.

A clear understanding of our target enabled us to concentrate on assembling inhibitors of PNP. Consequently, in the late 1980s, we formed a design group that included the three of us and Ealick, along with Mark E. Erion and Wayne C. Guida of Ciba-Geigy in Summit, N.J., Y. Sudhakar Babu of BioCryst and John A. Secrist III of the Southern Research Institute in Birmingham, Ala. This assembly was rather small compared with the armies of chemists and pharmacologists that traditionally have been required to screen and synthesize drug candidates.

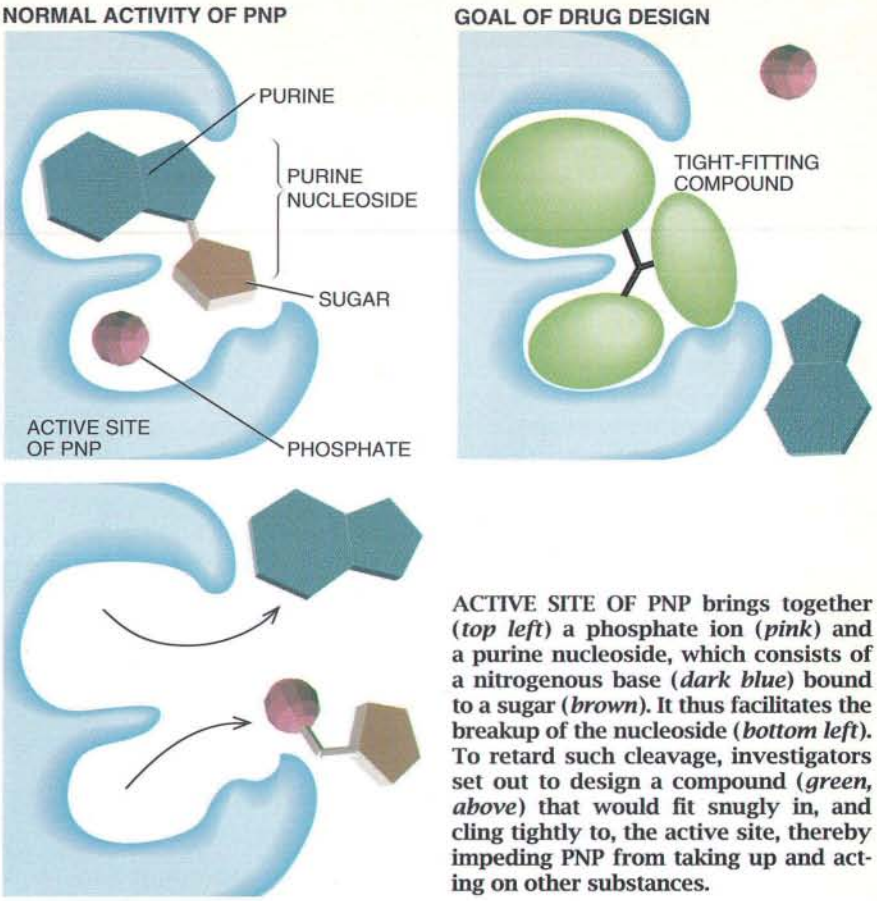
We focused initially on filling the purine binding region of the active site. That done, we planned to attend to the sugar binding region and, finally, the phosphate binding area. We expected that each successive step, which moved us closer toward fully occupying the active region, would enhance the affinity of a drug candidate for the enzyme.

From our crystallographic examinations, we knew that three amino acids in the purine binding pocket of PNP form hydrogen bonds with purines and their mimics. Such linkages are among the strongest reversible chemical bonds that exist. (Hydrogen bonds consist of two atoms, usually two nitrogens or one nitrogen and one oxygen, that share a hydrogen atom.) In proposing candidates for our inhibitor, then, we concentrated on compounds that, at the least, would form hydrogen bonds with the same three amino acids, all of which reside on a single monomer.

We thought we could achieve strong binding by substituting a carbon atom for a specific nitrogen atom in the purine guanine. Guanine consists of a combination of five carbon and four nitrogen atoms, arranged into two adjacent rings. (Each carbon and nitrogen in the rings is assigned a number from one to nine.) From the rings protrude several hydrogen atoms, a single amino group (NH_2) and one oxygen atom [*see a in box on next page*]. In particular, we favored exchanging a carbon atom for the nitrogen atom that normally occupies position nine. This choice appealed to us because we knew from earlier studies that such a change promotes binding to PNP. Guanine modified in this way is referred to as 9-deazaguanine; the number indicates the site of change, and the term "deaza" means without nitrogen.

We further expected that attaching an amino group to the carbon atom in position eight on our altered guanine molecule would enhance the purine's affinity for PNP. After all, the most potent membrane-permeable inhibitor of PNP available in the 1980s incorporated an amino group at exactly that position.

Taking a stepwise approach, we made one change at a time in the purine part of potential inhibitors. Then we tested the activity of the resulting molecules by examining their ability to block PNP from catalyzing the cleavage of nucleosides in the test tube. As we anticipated, substitution of carbon for the nitrogen in position nine of guanine resulted in an inhibitor that blocked PNP quite well. But, to our disappointment, adding the second change to the first one did not yield the superior inhibitor



ACTIVE SITE OF PNP brings together (*top left*) a phosphate ion (*pink*) and a purine nucleoside, which consists of a nitrogenous base (*dark blue*) bound to a sugar (*brown*). It thus facilitates the breakup of the nucleoside (*bottom left*). To retard such cleavage, investigators set out to design a compound (*green, above*) that would fit snugly in, and cling tightly to, the active site, thereby impeding PNP from taking up and acting on other substances.

we expected. In fact, our best hope turned out to be quite a poor performer.

In the absence of detailed structural information, we would have been mystified as to why affixing the amino group to the carbon in position eight proved unhelpful. But crystallography quickly provided the explanation. We separately analyzed the structures of complexes formed by PNP and four different compounds [*see box below*]. The purine part of the compounds consisted either of pure guanine, the carbon-substituted form (9-deazaguanine), guanine carrying an extra amino group at position eight (8-aminoguanine) or the doubly modified guanine (8-amino-9-deazaguanine).

We saw that one of the three amino acids forming the guanine binding site of PNP—an asparagine in the 243rd position on the protein chain—interacts with guanine by forming one strong and one weaker hydrogen bond. At the same time, asparagine establishes a hydrogen bond with a neighboring amino acid, threonine 242. This bond stabilizes the linkage of asparagine to guanine.

The carbon-for-nitrogen switch in the 9-deaza variant favors association with PNP in a fairly straightforward way: it substitutes a strong hydrogen bond for the relatively weak one occurring between asparagine 243 and guanine. Formation of a simple 8-aminoguanine variant leads to tight binding in another way, by giving rise to an extra hydrogen bond between the purine and PNP. Specifically, a direct hydrogen bond arises between the added amino group and threonine 242.

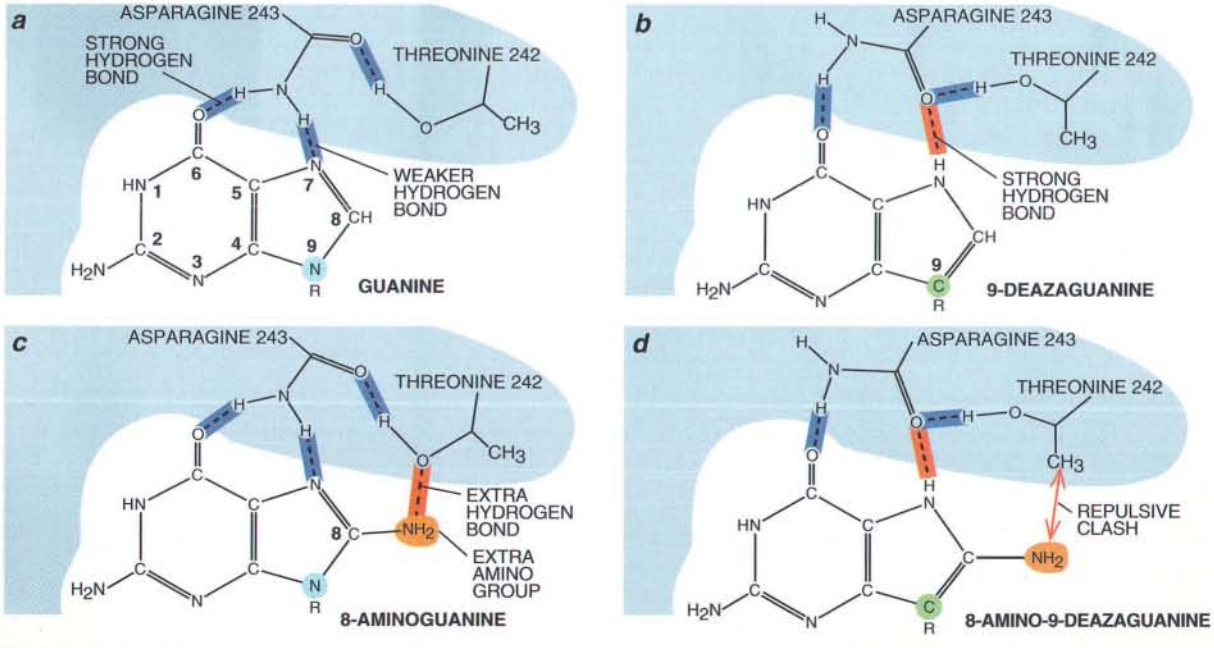
The combination of the two "improvements"—the carbon-for-nitrogen substitution and the addition of the amino group to position eight—was counterproductive because the carbon in position nine prevented the amino group at position eight from forming the extra bond with threonine 242. In fact, it set up an unfavorable, repulsive clash between the threonine and the added amino group.

Based on these findings, we immediately realized that pursuing inhibitors incorporating 8-amino-9-deazaguanine would be futile; 9-deazaguanine itself would be a better choice for the purine component of an inhibitor. This experience underscores the wonderful economy of the structure-based approach. As often happens to more conventional drug designers, we had headed directly into a blind alley. But our access to detailed structural information enabled us to retreat rapidly. Without crystallographic data, we might have pursued a logical but unproductive avenue of research much longer than we did.

The next task was to fill the sugar binding site. The sugar in a nucleoside does not attach to PNP primarily by forming hydrogen bonds. Rather more powerful hydrophobic attractions come into play. The hydrophobic effect is familiar to anyone who has ever watched oil separate out of salad dressing. Oily molecules have lit-

How a Design Mystery Was Solved

To create a molecule that would block the purine binding site of PNP, investigators made two changes in guanine, a purine. They expected that compounds carrying the resulting guanine derivative would bind tightly to PNP. But the strategy failed. Analyses of the chemical bonds in the complexes formed by the union of PNP with that and related guanine derivatives explained why. Guanine itself (*a*) forms two hydrogen bonds (*purple bands*) with the amino acid asparagine residing in position 243 of PNP. ("R" is rest of the compound.) Making one of the proposed changes in guanine—replacing nitrogen in position nine (*blue sphere*) with carbon (*green*), thus generating 9-deazaguanine (*b*)—enhanced affinity for PNP by causing a strong hydrogen bond (*red*) to replace the weaker one. Separately making the other proposed change in guanine (*c*)—substituting an amino group (*orange*) for the hydrogen bound to carbon in position eight—also improved guanine's affinity for PNP somewhat. It did so by causing an extra hydrogen bond to appear (between the amino group and threonine 242). Making both changes at once (*d*) yielded a poor inhibitor because the dual alteration led to a repulsive clash between threonine 242 and the amino group (*red arrow*). The exercise thus revealed that 9-deazaguanine would actually bind best.



tle affinity for water and are drawn to one another instead. The sugar binding pocket of PNP consists of three hydrophobic amino acids. Two of these amino acids (a phenylalanine and a tyrosine) come from the same monomer that binds guanine. The third (a phenylalanine) is contributed by the adjacent monomer.

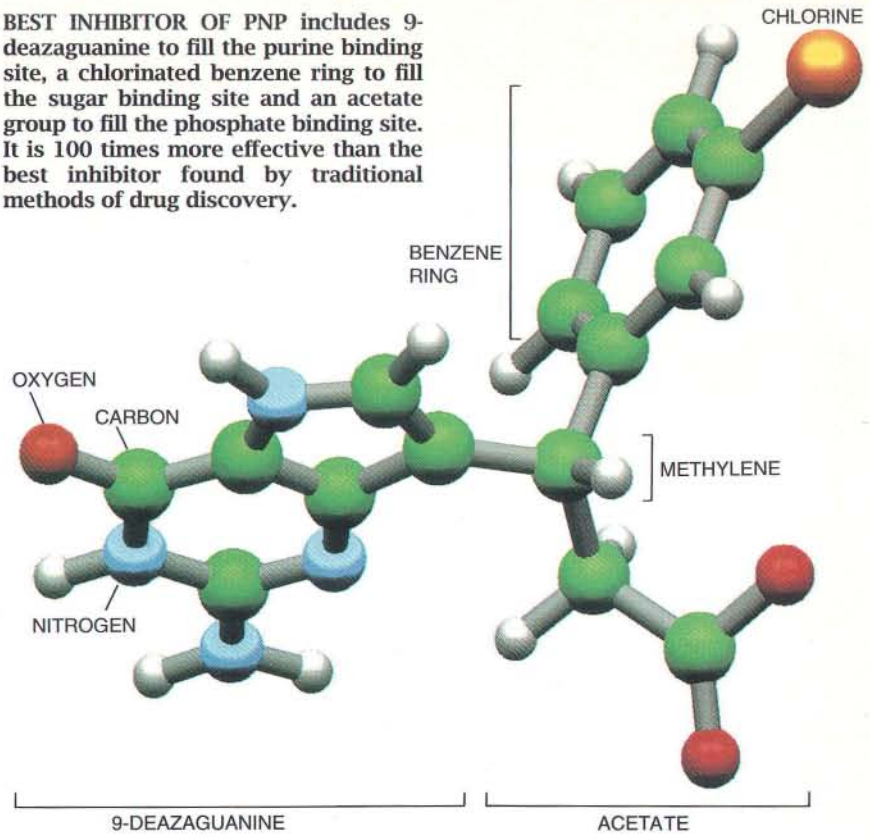
Several known inhibitors carried a benzene group (a ring formed by six carbon atoms and their associated hydrogens) in place of the sugar in nucleosides. (The sugar is attached to position nine of the purine.) Hence, we examined the inhibitory effect of an assemblage consisting of benzene linked to position nine (now a carbon atom) of 9-deazaguanine. The compound worked best when we joined the benzene group to 9-deazaguanine, not directly but through an intermediary: the carbon atom of a methylene group (CH_2). Still, we suspected we could do better.

On the computer screen, we saw that the sugar binding pocket could be filled more completely by adding any of several chemical groupings to the benzene ring. In reality, a few additions we tried were not good, for reasons we ascertained by crystallography. Others worked strikingly well, however. The best fit came from adding a chlorine atom to the carbon atom in position three of the benzene ring.

We had completed two thirds of our plan. The final step was adding a group that would interact with the phosphate binding site. We could not use phosphate itself, partly because phosphate-containing compounds have difficulty passing through cell membranes intact. Initial modeling studies encouraged us to prepare several structures that failed to improve the binding affinity of our two-part structure. Basically, chemical modifications that seemed reasonable on the computer screen gave rise in reality to substances that could not orient properly in the active site. Although we were disappointed, we were grateful that, once again, crystallography made it possible for us to discern the causes of the failure and to abandon doomed strategies. Indeed, information gleaned from crystallography helped us perform calculations enabling us to arrive at compounds that bound well to PNP.

For instance, calculations based on the crystallographic findings spurred us to add an acetate group (CH_2COO^-) to the methylene carbon atom that joined 9-deazaguanine to the chlorinated benzene ring. This step positioned the carboxyl segment (COO^-) of the acetate group so that it could lock on the phosphate binding site. The carboxyl unit is attracted to a positively charged

BEST INHIBITOR OF PNP includes 9-deazaguanine to fill the purine binding site, a chlorinated benzene ring to fill the sugar binding site and an acetate group to fill the phosphate binding site. It is 100 times more effective than the best inhibitor found by traditional methods of drug discovery.



amino acid in the active site of PNP.

When we tested the ability of the completed molecule to inhibit PNP, the results were gratifying. The compound blocked nucleoside cleavage 100 times more effectively than did any candidates in existence at that time. We were ecstatic. But would this compound—and others we assembled that were 10 to 20 times more potent than existing inhibitors—be useful in the body? To answer this question, we studied the ability of several of our molecules to protect the AIDS drug ddI from degradation by PNP in rats. All of them prolonged the half-life of this nucleoside mimic. Recent tests have shown that our PNP inhibitors can protect other nucleoside analogues and can suppress *T* cell functions in cultured cells and in experimental animals.

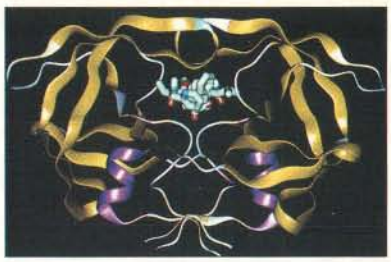
Our original goal of developing PNP inhibitors that could prolong the survival of synthetic nucleosides in animals, envisioned more than a decade earlier, had been accomplished. And it had been achieved less than three years after a small group of organic chemists began synthesizing candidates. In traditional practice, the invention of enzyme inhibitors often takes more than 10 years and can cost tens of millions of dollars. We needed to prepare only about 60 compounds in order to identify highly potent inhibitors, a small number in comparison to the hundreds or thousands of candidates that investigators using standard approaches generate.

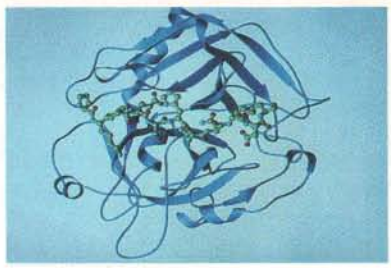
Researchers at the Washington University School of Medicine have recently completed two combined phase I and phase II clinical trials of one of our best inhibitors: BCX-34. These were small trials that looked at both safety and efficacy. Because the drug performed well against psoriasis and cutaneous *T* cell lymphoma, extended phase II (efficacy) trials have been planned by BioCryst. They may have already begun by the time these words are printed. Our most potent PNP inhibitor and its immediate relatives have been licensed to Ciba-Geigy for possible treatment of arthritis; these compounds are now being tested in animals.

We and others have had very satisfying experiences with structure-based drug design. Nevertheless, important stumbling blocks must be tackled if this strategy is to live up to its potential. At a fundamental level, the molecular interactions that give rise to disease are not always clear. In such cases, investigators may not be able to pinpoint the best targets to study.

Another obstacle relates to the fact that most drug targets are proteins. Although the techniques of molecular biology have made many proteins available in quantity, some of them are still

PROTEIN TARGET	DISEASES	DEVELOPERS
HIV protease	AIDS	Abbott Laboratories
HIV protease	AIDS	Merck Research Laboratories
Thymidylate synthase	Cancer, psoriasis	Agouron Pharmaceuticals
Thrombin	Blood clots	Biogen
Carbonic anhydrase	Ocular hypertension/ glaucoma	Merck Research Laboratories
Rhinovirus coat protein	Common cold	Sterling Winthrop





SOME PROMISING DRUGS created by structure-based design strategies are in clinical trials. Among them are inhibitors of an enzyme produced by the AIDS-causing virus, HIV (Abbott's version appears as spheres in the top photograph.) Another example is an inhibitor of the enzyme thrombin, designed to reduce blood clotting (*bottom photograph*).

difficult to obtain in pure form. Even where supply is not a problem, solving the structure of a protein continues to be difficult. Crystallography works beautifully if one has well-ordered crystals, but proteins as a group (and nucleic acids, too) are challenging to crystallize in forms suitable for high-resolution x-ray diffraction studies. Membrane-bound proteins, including various hormone receptors, are particularly recalcitrant; they are oily and cling to one another haphazardly.

Many protein crystallographers in pharmaceutical companies have begun to ameliorate the crystallization problem by turning to robotics. Robotic systems can automatically assess thousands of combinations of conditions under which crystallization occurs, suggesting optimal solutions. At the same time, the equipment for obtaining and interpreting x-ray diffraction images is improving, and techniques are being developed for determining the three-dimensional structure of large, noncrystallized proteins in their natural, aqueous environment. A method known as nuclear magnetic resonance spectroscopy (NMR) has been applied to solve the structures of some proteins, but none yet as big as PNP. That limitation may be overcome in the future.

One day researchers may be able to bypass crystallography and NMR altogether, deducing the three-dimensional structure of protein targets directly from their linear amino acid sequence. At the moment, though, the predictive ability of computer programs leaves something to be desired, both for solving the structure of a molecular target and for assessing the fit and attraction between a proposed drug and its target. Predictive accuracy is improving, however, as the theoretical underpinnings of existing programs expand. Eventually, computer analyses may lead workers directly to the best composition of a drug, freeing them from having to synthesize and test less effective, intermediary compounds. The ideal would be to make the best drug on the first try, be it from scratch or through the alteration of an existing substance.

Although this goal remains distant, our development of powerful inhibitors of PNP, and the parallel invention of different enzyme inhibitors by other structural chemists, demonstrates that, perfect or not, structure-based drug design is already quite useful. Among the drug candidates now in clinical trials are two created separately at Abbott Laboratories and at Merck Research Laboratories. These drugs inhibit an enzyme made by the AIDS-causing human immunodeficiency virus (HIV). This enzyme, a protease, is required for the accurate assembly of viral particles and for their spread from cell to cell. The structural approach enabled the drugs to reach human testing in less than four years.

Agouron has engineered enzyme blockers now being studied in cancer patients. These drugs inhibit thymidilate synthase, which participates in synthesis of the nucleotides cancer cells need in order to replicate their DNA and proliferate. And an inhibitor developed by Merck is being examined for its ability to combat glaucoma by interfering with the enzyme carbonic anhydrase. Merck is also working on a drug, not yet in clinical trials, to treat emphysema. It shuts off human neutrophil elastase, an enzyme that has been implicated in damaging lung tissue; human neutrophil elastase may also contribute to rheumatoid arthritis and acute respiratory distress syndrome.

Twelve years ago just one pharmaceutical house in the U.S.—Merck—had assembled a team of investigators dedicated to structure-based drug design. Today most large drugmakers in this country employ such teams, as do various other companies around the world. Several corporations that rely mainly on this method are emerging on the American pharmaceutical landscape. All indications suggest that structure-based drug design is here to stay and will make a major contribution to the drugs brought to market in the years to come.

FURTHER READING

APPLICATION OF CRYSTALLOGRAPHIC AND MODELING METHODS IN THE DESIGN OF PURINE NUCLEOSIDE PHOSPHORYLASE INHIBITORS. S. E. Ealick, Y. S. Babu, C. E. Bugg, M. D. Erion, W. C. Guida, J. A. Montgomery and J. A. Secrist III in *Proceedings of the National Academy of Sciences*, Vol. 88, No. 24, pages 11540–11544; December 15, 1991.

APPLICATION OF CRYSTALLOGRAPHY TO THE DESIGN OF ANTIVIRAL AGENTS. M. G. Rossmann and M. A. McKinlay in *Infectious Agents and Disease*, Vol. 1, No. 1, pages 3–10; February 1992.

USE OF STRUCTURAL INFORMATION IN DRUG DESIGN. M. A. Navia and M. A. Murcko in *Current Opinion in Structural Biology*, Vol. 2, No. 2, pages 202–210; April 1992.

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Coupled Oscillators and Biological Synchronization

A subtle mathematical thread connects clocks, ambling elephants, brain rhythms and the onset of chaos

by Steven H. Strogatz and Ian Stewart

In February 1665 the great Dutch physicist Christiaan Huygens, inventor of the pendulum clock, was confined to his room by a minor illness. One day, with nothing better to do, he stared aimlessly at two clocks he had recently built, which were hanging side by side. Suddenly he noticed something odd: the two pendulums were swinging in perfect synchrony.

He watched them for hours, yet they never broke step. Then he tried disturbing them—within half an hour they regained synchrony. Huygens suspected that the clocks must somehow be influencing each other, perhaps through tiny air movements or imperceptible vibrations in their common support. Sure enough, when he moved them to opposite sides of the room, the clocks gradually fell out of step, one losing five seconds a day relative to the other.

Huygens's fortuitous observation initiated an entire subbranch of mathematics: the theory of coupled oscillators. Coupled oscillators can be found throughout the natural world, but they are especially conspicuous in living things: pacemaker cells in the heart; insulin-secreting cells in the pancreas; and neural networks in the brain and spinal cord that control such rhythmic behaviors as breathing, running and chewing. Indeed, not all the oscillators need be confined to the same organism: consider crickets that chirp in unison and congregations of synchronously flashing fireflies [see "Synchronous Fireflies," by John and Elisabeth Buck; SCIENTIFIC AMERICAN, May 1976].

Since about 1960, mathematical biologists have been studying simplified models of coupled oscillators that retain the essence of their biological prototypes. During the past few years, they have made rapid progress, thanks to breakthroughs in computers and computer graphics, collaborations with experimentalists who are open to theory, ideas borrowed from physics and new developments in mathematics itself.

To understand how coupled oscillators work together, one must first understand how one oscillator works by itself. An oscillator is any system that executes periodic behavior. A swinging pendulum, for example, returns to the same point in space at regular intervals; furthermore, its velocity also rises and falls with (clockwork) regularity.

Instead of just considering an oscillator's behavior over time, mathematicians are interested in its motion through phase space. Phase space is an abstract space whose coordinates describe the state of the system. The motion of a pendulum in phase space, for instance, would be drawn by releasing the pendulum at various heights and then plotting its position and velocity. These trajectories in phase space turn out to be closed curves, because the pendulum, like any other oscillator, repeats the same motions over and over again.

A simple pendulum consisting of a weight at the end of a string can take any of an infinite number of closed paths through phase space, depending on the height from which it is released. Biological systems (and clock pendulums), in contrast, tend to have not only a characteristic period but also a characteristic amplitude. They trace a particular path through phase space, and if some perturbation jolts them out of their accustomed rhythm they soon return to their former path. If someone startles you, say, by shouting, "Boo!", your heart may start pounding but soon relaxes to its normal behavior.

Oscillators that have a standard waveform and amplitude to which they return after small perturbations are known as limit-cycle oscillators. They incorporate a dissipative mechanism to damp oscillations that grow too large and a source of energy to pump up those that become too small.

A single oscillator traces out a simple path in phase space. When two or more oscillators are coupled, however, the range of possible behaviors becomes much more complex. The equations governing their behavior tend to become intractable. Each oscillator may be coupled only to a few immediate neighbors—as are the neuromuscular oscillators in the small intestine—or it could be coupled to all the oscillators in an enormous community. The situation mathematicians find

THOUSANDS OF FIREFLIES flash in synchrony in this time exposure of a nocturnal mating display. Each insect has its own rhythm, but the sight of its neighbors' lights brings that rhythm into harmony with those around it. Such couplings among oscillators are at the heart of a wide variety of natural phenomena.

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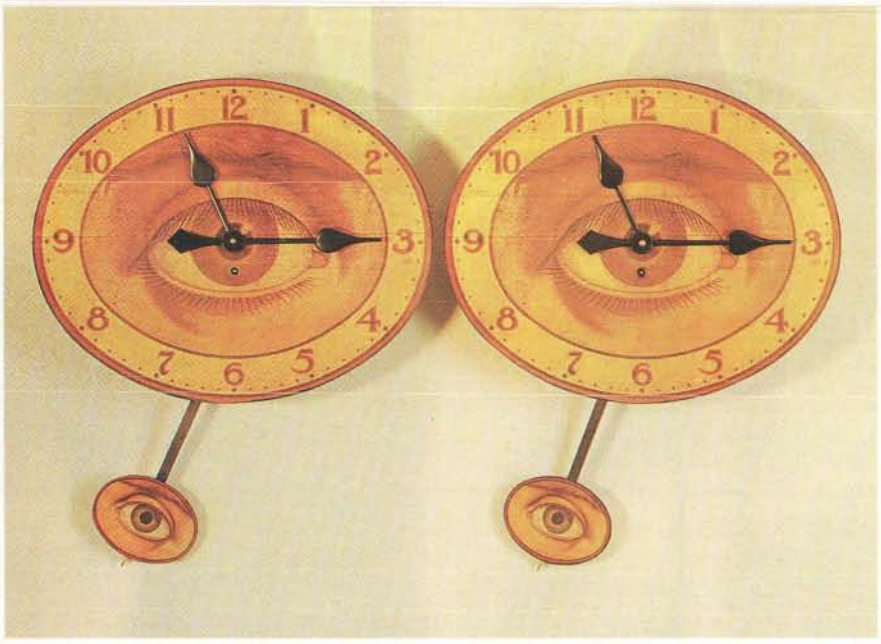


PENDULUM CLOCKS placed near each other soon become synchronized (*above*) by tiny coupling forces transmitted through the air or by vibrations in the wall to which they are attached. Dutch physicist Christiaan Huygens invented the pendulum clock and was the first to observe this phenomenon, inaugurating the study of coupled oscillators.

easiest to describe arises when each oscillator affects all the others in the system and the force of the coupling increases with the phase difference between the oscillators. In this case, the interaction between two oscillators that are moving in synchrony is minimal.

Indeed, synchrony is the most familiar mode of organization for coupled oscillators. One of the most spectacular examples of this kind of coupling can be seen along the tidal rivers of Malaysia, Thailand and New Guinea, where thousands of male fireflies gather in trees at night and flash on and off in unison in an attempt to attract the females that cruise overhead. When the males arrive at dusk, their flickerings are uncoordinated. As the night deepens, pockets of synchrony begin to emerge and grow. Eventually whole trees pulsate in a silent, hypnotic concert that continues for hours.

Curiously, even though the fireflies' display demonstrates coupled oscillation on a grand scale, the details of this behavior have long resisted mathematical analysis. Fireflies are a paradigm of a "pulse coupled" oscillator system: they interact only when one sees the sudden flash of another and shifts its rhythm accordingly. Pulse coupling is common in biology—consider crickets chirping or neurons communicating via electrical spikes called action potentials—but the impulsive character of the coupling has rarely been included in mathematical models. Pulse coupling is awkward to handle mathematically because it introduces discontinuous behavior into an otherwise continuous model and so stymies most of the standard mathematical techniques.

Recently one of us (Strogatz), along with Renato E. Mirollo of Boston College, created an idealized mathematical model of fireflies and other pulse-coupled oscillator systems. We proved that under certain circumstances, oscillators started at different times will always become synchronized [see "Electronic Fireflies," by Wayne Garver and Frank Moss, "The Amateur Scientist," page 94].

Our work was inspired by an earlier study by Charles S. Peskin of New York University. In 1975 Peskin proposed a highly schematic model of the heart's natural pacemaker, a cluster of about 10,000 cells called the sinoatrial node. He hoped to answer the question of how these cells synchronize their individual electrical rhythms to generate a normal heartbeat.

Peskin modeled the pacemaker as a large number of identical oscillators, each coupled equally strongly to all the others. Each oscillator is based on an electrical circuit consisting of a capacitor in parallel with a resistor. A constant input current causes the voltage across the capacitor to increase steadily. As the voltage rises, the amount of current passing through the resistor increases, and so the rate of increase slows down. When the voltage reaches a threshold, the capacitor discharges, and the voltage drops instantly to zero—this pattern mimics the firing of a pacemaker cell and its subsequent return to baseline. Then the voltage starts rising again, and the cycle begins anew.

A distinctive feature of Peskin's model is its physiologically plausible form of pulse coupling. Each oscillator affects the others only when it fires. It kicks their voltage up by a fixed amount; if any cell's voltage exceeds the threshold, it fires immediately. With these rules in place, Peskin stated two provocative conjectures: first, the system would always eventually become synchronized; second, it would synchronize even if the oscillators were not quite identical.

When he tried to prove his conjectures, Peskin ran into technical roadblocks. There were no established mathematical procedures for handling arbitrarily large systems of oscillators. So he backed off and focused on the simplest possible case: two identical oscillators. Even here the mathematics was thorny. He restricted the problem further by allowing only infinitesimal kicks and infinitesimal leakage through the resistor. Now the problem became manageable—for this special case, he proved his first conjecture.

Peskin's proof relies on an idea introduced by Henri Poincaré, a virtuoso French mathematician who lived in the early 1900s. Poincaré's concept is the mathematical equivalent of stroboscopic photography. Take two identical pulse-coupled oscillators, *A* and *B*, and

chart their evolution by taking a snapshot every time *A* fires.

What does the series of snapshots look like? *A* has just fired, so it always appears at zero voltage. The voltage of *B*, in contrast, changes from one snapshot to the next. By solving his circuit equations, Peskin found an explicit but messy formula for the change in *B*'s voltage between snapshots. The formula revealed that if the voltage is less than a certain critical value, it will decrease until it reaches zero, whereas if it is larger, it will increase. In either case, *B* will eventually end up synchronized with *A*.

There is one exception: if *B*'s voltage is precisely equal to the critical voltage, then it can be driven neither up nor down and so stays poised at criticality. The oscillators fire repeatedly about half a cycle out of phase from each other. But this equilibrium is unstable, like a pencil balancing on its point. The slightest nudge tips the system toward synchrony.

Despite Peskin's successful analysis of the two-oscillator case, the case of an arbitrary number of oscillators eluded proof for about 15 years. In 1989 Strogatz learned of Peskin's work in a book on biological oscillators by Arthur T. Winfree of the University of Arizona. To gain intuition about the behavior of Peskin's model, Strogatz wrote a computer program to simulate it for any number of identical oscillators, for any kick size and for any amount of leakage. The results were unambiguous: the system always ended up firing in unison.

Excited by the computer results, Strogatz discussed the problem with Mirollo. They reviewed Peskin's proof of the two-oscillator case and noticed that it could be clarified by using a more abstract model for the individual oscillators. The key feature of the model turned out to be the slowing upward curve of voltage (or its equivalent) as it rose toward the firing threshold. Other characteristics were unimportant.

Mirollo and Strogatz proved that their generalized system always becomes synchronized, for any number of oscillators and for almost all initial conditions. The proof is based on the notion of "absorption"—a shorthand for the idea that if one oscillator kicks another over threshold, they will remain synchronized forever. They have identical dynamics, after all, and are identically coupled to all the others. The two were able to show that a sequence of absorptions eventually locks all the oscillators together.

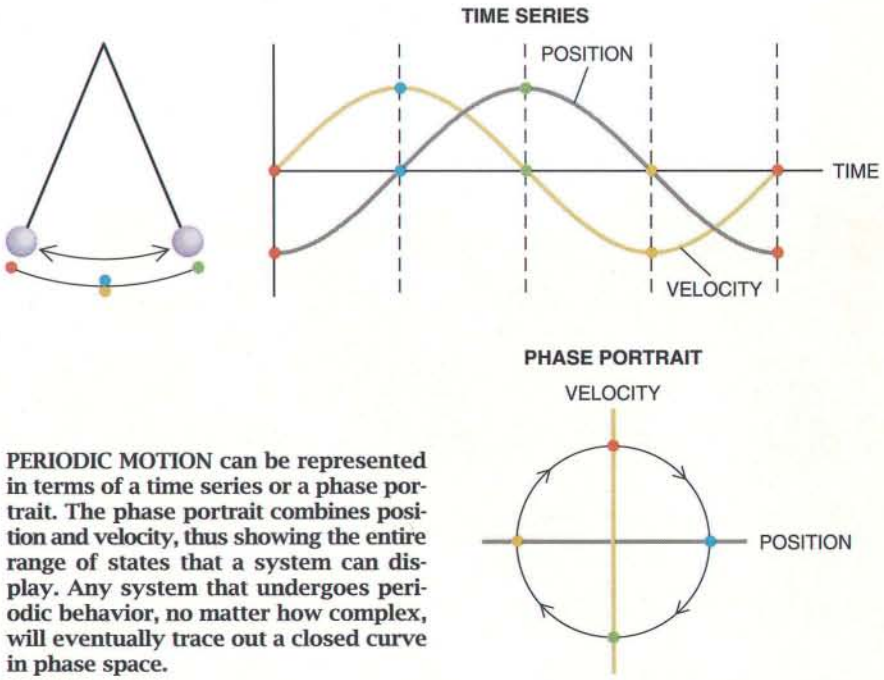
Although synchrony is the simplest state for coupled identical oscillators, it is not inevitable. Indeed, coupled oscillators often fail to synchronize. The explanation is a phenomenon known as symmetry breaking, in which a single symmetric state—such as synchrony—is replaced by several less symmetric states that together embody the original symmetry. Coupled oscillators are a rich source of symmetry breaking.

Synchrony is the most obvious case of a general effect called phase locking: many oscillators tracing out the same pattern but not necessarily in step. When two identical oscillators are coupled, there are exactly two possibilities: synchrony, a phase difference of zero, and antisynchrony, a phase difference of one half. For example, when a kangaroo hops across the Australian outback, its powerful hind legs oscillate periodically, and both hit the ground at the same instant. When a human runs after the kangaroo, meanwhile, his legs hit the ground alternately. If the network has more than two oscillators, the range of possibilities increases. In 1985 one of us (Stewart), in collaboration with Martin Golubitsky of the University of Houston, developed a mathematical classification of the patterns of networks of coupled oscillators, following earlier work by James C. Alexander of the University of Maryland and Giles Auchmuty of the University of Houston.

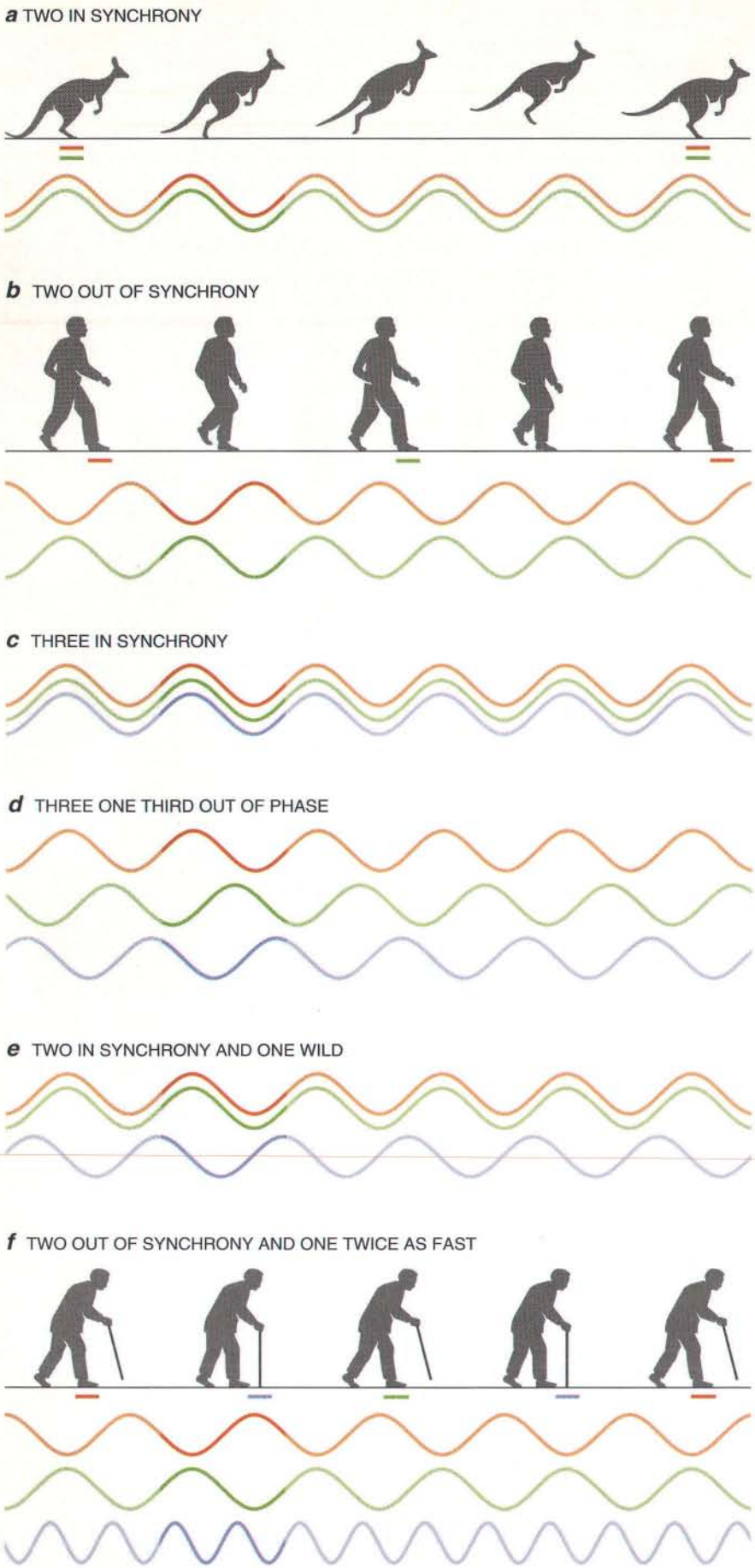
The classification arises from group theory (which deals with symmetries in a collection of objects) combined with Hopf bifurcation (a generalized description of how oscillators "switch on"). In 1942 Eberhard Hopf established a general description of the onset of oscillation. He started by considering systems that have a rest point in phase space (a steady state) and seeing what happened when one approximated their motion near that point by a simple linear function. Equations describing certain systems behave in a peculiar fashion as the system is driven away from its rest point. Instead of either returning slowly to equilibrium or moving rapidly outward into instability, they oscillate. The point at which this transition takes place is termed a bifurcation because the system's behavior splits into two branches—an unstable rest state coexists with a stable oscillation. Hopf proved that systems whose linearized form undergoes this type of bifurcation are limit-cycle oscillators: they have a preferred waveform and amplitude. Stewart and Golubitsky showed that Hopf's idea can be extended to systems of coupled identical oscillators, whose states undergo bifurcations to produce standard patterns of phase locking.

For example, three identical oscillators coupled in a ring can be phase-locked in four basic patterns. All oscillators can move synchronously; successive oscillators around the ring can move so that their phases differ by one third; two oscillators can move synchronously while the third moves in an unrelated manner (except that it oscillates with the same period as the others); and two oscillators may be moving half a phase out of step, while the third oscillates twice as rapidly as its neighbors.

The strange half-period oscillations that occur in the fourth pattern were a



PERIODIC MOTION can be represented in terms of a time series or a phase portrait. The phase portrait combines position and velocity, thus showing the entire range of states that a system can display. Any system that undergoes periodic behavior, no matter how complex, will eventually trace out a closed curve in phase space.



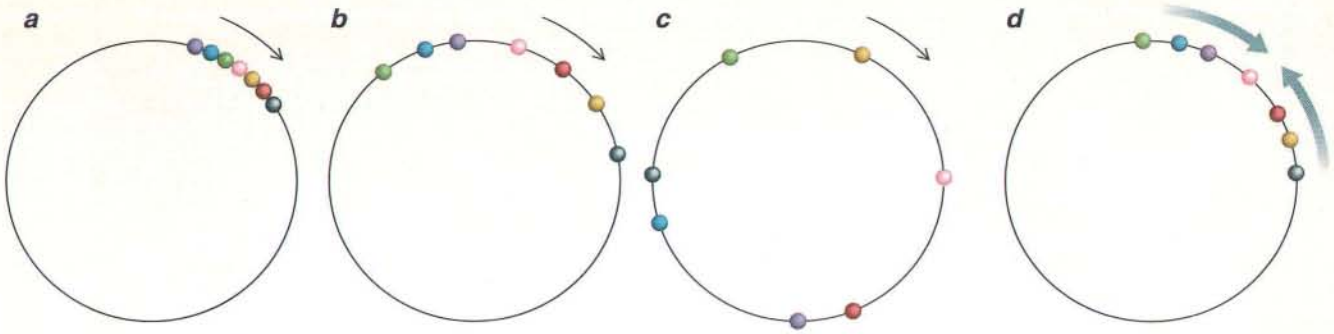
surprise at first, even to Stewart and Golubitsky, but in fact the pattern occurs in real life. A person using a walking stick moves in just this manner: right leg, stick, left leg, stick, repeat. The third oscillator is, in a sense, driven by the combined effects of the other two: every time one of them hits a peak, it gives the third a push. Because the first two oscillators are precisely antisynchronous, the third oscillator peaks twice while the others each peak once.

The theory of symmetrical Hopf bifurcation makes it possible to classify the patterns of phase locking for many different networks of coupled oscillators. Indeed, Stewart, in collaboration with James J. Collins, a biomedical engineer at Boston University, has been investigating the striking analogies between these patterns of phase locking and the symmetries of animal gaits, such as the trot, pace and gallop.

Quadruped gaits closely resemble the natural patterns of four-oscillator systems. When a rabbit bounds, for example, it moves its front legs together, then its back legs. There is a phase difference of zero between the two front legs and of one half between the front and back legs. The pace of a giraffe is similar, but the front and rear legs on each side are the ones that move together. When a horse trots, the locking occurs in diagonal fashion. An ambling elephant lifts each foot in turn, with phase differences of one quarter at each stage. And young gazelles complete the symmetry group with the pronk, a four-legged leap in which all legs move in synchrony [see "Mathematical Recreations," by Ian Stewart; SCIENTIFIC AMERICAN, April 1991].

More recently, Stewart and Collins have extended their analysis to the hexapod motion of insects. The tripod

SYMMETRY BREAKING governs the ways that coupled oscillators can behave. Synchrony is the most symmetrical single state, but as the strength of the coupling between oscillators changes, other states may appear. Two oscillators can couple in either synchronous or antisynchronous fashion (*a*, *b*), corresponding roughly to the bipedal locomotion of a kangaroo or a person. Three oscillators can couple in four ways: synchrony (*c*), each one third of a cycle out of phase with the others (*d*), two synchronous and one with an unrelated phase (*e*) or in the peculiar rhythm of two oscillators antisynchronous and the third running twice as fast (*f*). This pattern is also the gait of a person walking slowly with the aid of a stick.



NONIDENTICAL OSCILLATORS may start out in phase with one another (as shown on circle *a*, in which 360 degrees mark one oscillation), but they lose coherence as the faster ones move ahead, and the slower ones fall behind (*b, c*). A simple coupling force that speeds up slower oscillators and slows down faster ones, however, can keep them all in phase (*d*).

gait of a cockroach is a very stable pattern in a ring of six oscillators. A triangle of legs moves in synchrony: front and back left and middle right; then the other three legs are lifted with a phase difference of one half.

Why do gaits resemble the natural patterns of coupled oscillators in this way? The mechanical design of animal limbs is unlikely to be the primary reason. Limbs are not passive mechanical oscillators but rather complex systems of bone and muscle controlled by equally complicated nerve assemblies. The most likely source of this concordance between nature and mathematics is in the architecture of the circuits in the nervous system that control locomotion. Biologists have long hypothesized the existence of networks of coupled neurons they call central pattern generators, but the hypothesis has always been controversial. Nevertheless, neurons often act as oscillators, and so, if central pattern generators exist, it is reasonable to expect their dynamics to resemble those of an oscillator network.

Moreover, symmetry analysis solves a significant problem in the central-pattern generator hypothesis. Most animals employ several gaits—horses walk, trot, canter and gallop—and biologists have often assumed that each gait requires a separate pattern generator. Symmetry breaking, however, implies that the same central-pattern generator circuit can produce all of an animal's gaits. Only the strength of the couplings among neural oscillators need vary.

So far our analysis has been limited to collections of oscillators that are all strictly identical. That idealization is convenient mathematically, but it ignores the diversity that is always present in biology. In any real population, some oscillators will always be inherently faster or slower. The behavior of communities of oscillators whose members have differing frequencies depends on the strength of the coupling among them. If their interactions are too weak, the oscillators will be unable to achieve synchrony. The result is incoherence, a cacophony of oscillations. Even if started in unison the oscillators will gradually drift out of phase, as did Huygens's pendulum clocks when placed at opposite ends of the room.

Colonies of the bioluminescent algae *Gonyaulax* demonstrate just this kind of desynchronization. J. Woodland Hastings and his colleagues at Harvard University have found that if a tank full of *Gonyaulax* is kept in constant dim light in a laboratory, it exhibits a circadian glow rhythm with a period close to 23 hours. As time goes by, the waveform broadens, and this rhythm gradually damps out. It appears that the individual cells continue to oscillate, but they drift out of phase because of differences in their natural frequencies. The glow of the algae themselves does not maintain synchrony in the absence of light from the sun.

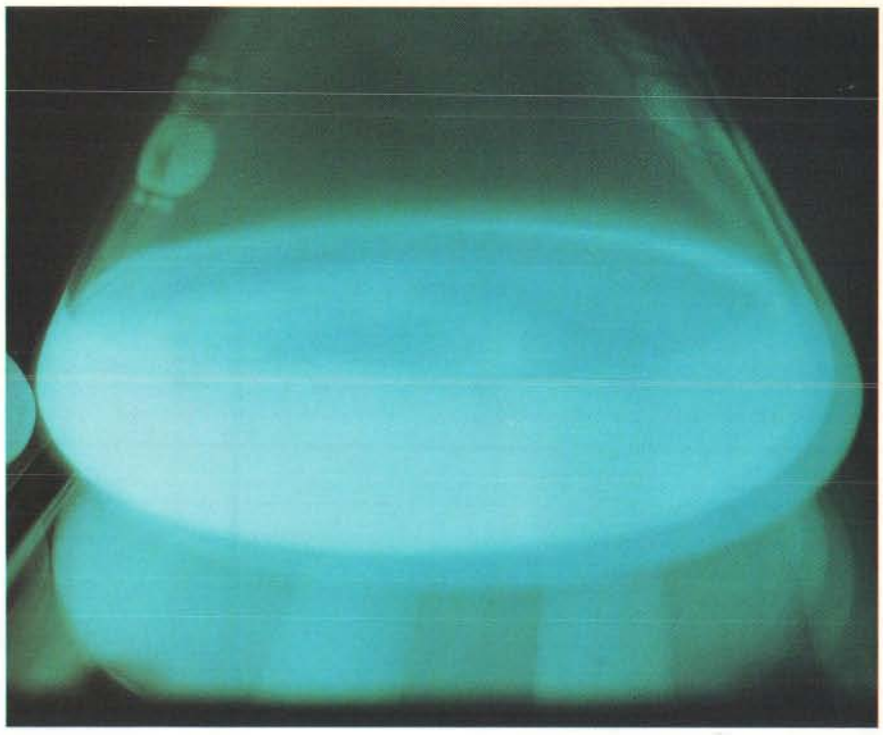
In other oscillator communities the coupling is strong enough to overcome the inevitable differences in natural frequency. Polymath Norbert Wiener pointed out in the late 1950s that such oscillator communities are ubiquitous in biology and indeed in all of nature. Wiener tried to develop a mathematical model of collections of oscillators, but his approach has not turned out to be fruitful. The theoretical breakthrough came in 1966, when Winfree, then a graduate student at Princeton University, began exploring the behavior of large populations of limit-cycle oscillators. He used an inspired combination of computer simulations, mathematical analysis and experiments on an array of 71 electrically coupled neon-tube oscillators.

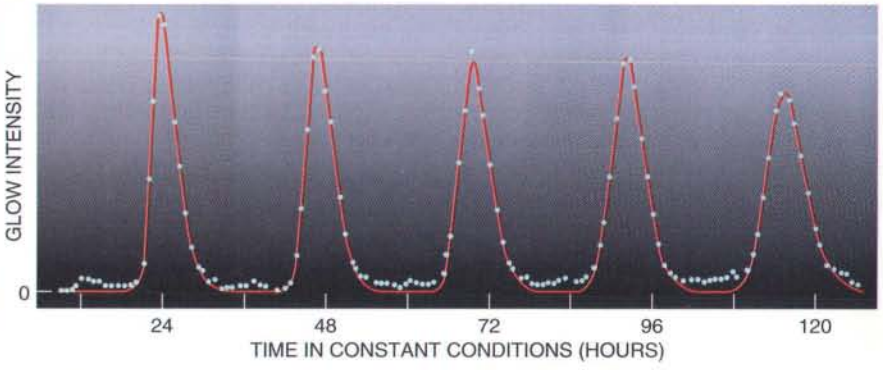
Winfree simplified the problem tremendously by pointing out that if oscillators are weakly coupled, they remain close to their limit cycles at all times. This insight allowed him to ignore variations in amplitude and to consider only their variations in phase. To incorporate differences among the oscillators, Winfree made a model that captured the essence of an oscillator community by assuming that their natural frequencies are distributed according to a narrow probability function and that in other respects the oscillators are identical. In a final and crucial simplification, he assumed that each oscillator is influenced only by the collective rhythm produced by all the others. In the case of fireflies, for example, this would mean that each firefly responds to the collective flash of the whole population rather than to any individual firefly.

To visualize Winfree's model, imagine a swarm of dots running around a circle. The dots represent the phases of the oscillators, and the circle represents their common limit cycle. If the oscillators were independent, all the dots would eventually disperse over the circle, and the collective rhythm would decay to zero. Incoherence reigns. A simple rule for interaction among oscillators can restore coherence, however: if an oscillator is ahead of the group, it slows down a bit; if it is behind, it speeds up.

In some cases, this corrective coupling can overcome the differences in natural frequency; in others (such as that of *Gonyaulax*), it cannot. Winfree found that the system's behavior depends on the width of the frequency distribution. If the spread of frequencies is large compared with the coupling, the system always lapses into incoherence, just as if it were not coupled at all. As the spread decreases below a critical value, part of the system spontaneously "freezes" into synchrony.

Synchronization emerges cooperatively. If a few oscillators happen to synchronize, their combined, coherent signal rises above the background din, exerting a stronger effect on the others.





***GONYAULAX* luminescent algae (*top*) change the intensity of their glow according to an internal clock that is affected by light. If they are kept in constant dim light, the timing of the glow becomes less precise because the coupling among individual organisms is insufficient to keep them in sync (*bottom*).**

When additional oscillators are pulled into the synchronized nucleus, they amplify its signal. This positive feedback leads to an accelerating outbreak of synchrony. Some oscillators nonetheless remain unsynchronized because their frequencies are too far from the value at which the others have synchronized for the coupling to pull them in.

In developing his description, Winfree discovered an unexpected link between biology and physics. He saw that mutual synchronization is strikingly analogous to a phase transition such as the freezing of water or the spontaneous magnetization of a ferromagnet. The width of the oscillators' frequency distribution plays the same role as does temperature, and the alignment of oscillator phases in time is the counterpart of an alignment of molecules or electronic spins in space.

The analogy to phase transitions opened a new chapter in statistical mechanics, the study of systems composed of enormous numbers of interacting subunits. In 1975 Yoshiki Kuramoto of Kyoto University presented an elegant reformulation of Winfree's model. Kuramoto's model has a simpler mathematical structure that allows it to be analyzed in great detail. Recently Strogatz, along with Mirollo and Paul C. Matthews of the University of Cambridge, found an unexpected connection between Kuramoto's model and Landau damping, a puzzling phenomenon that arises in plasma physics when electrostatic waves propagate through a highly rarefied medium. The connection emerged when we

studied the decay to incoherence in oscillator communities in which the frequency distribution is too broad to support synchrony. The loss of coherence, it turns out, is governed by the same mathematical mechanism as that controlling the decay of waves in such "collisionless" plasmas.

The theory of coupled oscillators has come a long way since Huygens noticed the spontaneous synchronization of pendulum clocks. Synchronization, apparently a very natural kind of behavior, turns out to be both surprising and interesting. It is a problem to understand, which is not an obvious consequence of symmetry. Mathematicians have turned to the theory of symmetry breaking to classify the general patterns that arise when identical, ostensibly symmetric oscillators are coupled. Thus, a mathematical discipline that has its most visible roots in particle physics appears to govern the leap of a gazelle and the ambling of an elephant. Meanwhile techniques borrowed from statistical mechanics illuminate the behavior of entire populations of oscillators. It seems amazing that there should be a link between the violent world of plasmas, where atoms routinely have their electrons stripped off, and the peaceful world of biological oscillators, where fireflies pulse silently along a riverbank. Yet there is a coherent mathematical thread that leads from the simple pendulum to spatial patterns, waves, chaos and phase transitions. Such is the power of mathematics to reveal the hidden unity of nature.

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The Death Cults of Prehistoric Malta

New archaeological excavations reveal that as the ancient island societies suffered from environmental decline, they developed an extreme religious preoccupation with life and death

by Caroline Malone, Anthony Bonanno, Tancred Gouder, Simon Stoddart and David Trump

The Mediterranean region is a fine laboratory for the scientific study of early religions because so many emerged there. Everyone has heard of the mythology of Greece and the cults surrounding the Roman emperors. Yet those were the religions of city-states not far removed from our own modern societies. Far less well known are the religions of the agricultural communities that preceded the advance of Greco-Roman civilization.

In several of the latter, images of corpulent human figures played an important role. Because some of these figures are recognizably female in shape, archaeologists sometimes refer to them as "fat ladies" and associate them with the celebration of fertility, both human and agricultural. On one small group of islands, those of Malta, such figures became the object of an infatuation that was closely linked to the construction of the earliest free-standing public stone buildings in the world.

Those temples and the underground burial chambers related to them contained many images of obese humans—some no larger than a few centimeters, others the size of giants—as well as of animals and phallic symbols. A collaborative project between British and Maltese archaeologists, of which we are the directors, has recently made spectacular discoveries about the artistic representations of the so-called mother goddesses. These findings have cast new light on how certain religious practices evolved on Malta and perhaps on why they eventually disappeared. They suggest the religion itself encompassed much more than a worship of human fecundity. They also tell a cautionary tale about what happens when a people focus too much energy on worshiping life rather than sustaining it.

Traditionally, archaeological discoveries in Malta have been interpreted—or perhaps we should say misinterpreted—against a backdrop of broad conjecture about the significance of mother goddesses. Figurines fitting that general description date from the Upper Paleolithic era (about 25,000 years ago) to the dawn of metal-using societies in the Neolithic era. A few have been found in western Europe, but the yields have been much richer at sites in Egypt, the Levant, Turkey, Greece, Cyprus and the Balkans. The most elaborate figures come from the islands of Malta in the third millennium B.C.

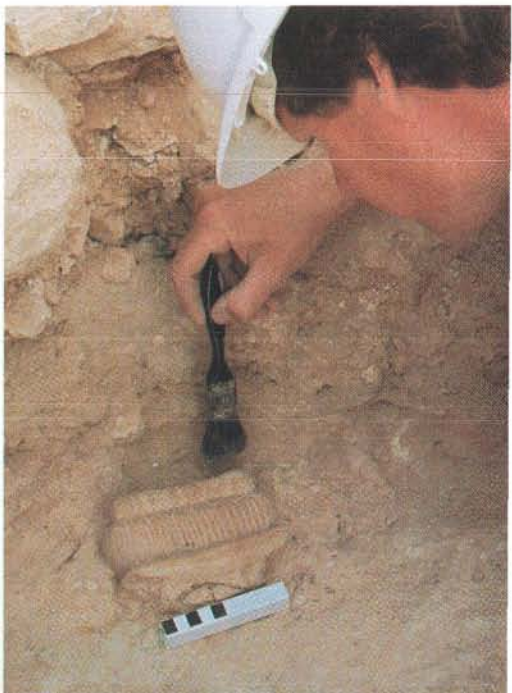
Unfortunately, many of these figurines are far less informative than they might once have been because of the unscientific ways in which they were collected. The dating of the figures is often inaccurate. The records of where and how they were situated are often incomplete, so we cannot know whether the figures were peculiar to burial sites, shrines or houses. We do know that in the Balkans such figures were kept in houses inside specially constructed niches in the walls. In Turkey, at the site of the eighth millenium B.C. settlement Çatal Hüyük, the finest figurines of clay and stone were associated with the burials of high-status people in special shrines, whereas cruder figurines were found in houses.

The discovery of similar figurines at far-flung sites and from disparate eras inspired a long tradition of scholarly speculation about a widespread prehistoric religion based on the worship of the mother goddess. In the middle decades of this century, for example, some archaeologists tried to show that a cult of the Eye Goddess (so called because of eye motifs on Mesopotamian idols) diffused throughout the entire Mediterranean. More recently, claims have been made that the Balkans were the center of an Old European religion.

Most modern scholars appreciate that the early cults were radically different in each prehistoric society and that the

CAROLINE MALONE, ANTHONY BONANNO, TANCRED GOUDER, SIMON STODDART and DAVID TRUMP have extensively explored the ruins of ancient Maltese culture and contributed to the modern understanding of it. Malone and Stoddart are both lecturers in archaeology at the University of Bristol in England. Bonanno is professor of archaeology at the University of Malta. Gouder is director of museums at the National Museum of Malta. Trump is a lecturer in extramural studies at the University of Cambridge. Between 1958 and 1963 he was also curator of archaeology at the University of Malta.

SEATED PAIR of human figures (*opposite page*) is helping archaeologists revise their views of Maltese prehistory. The statue was unearthed (*below*) from a subterranean burial complex on the island of Gozo.



cults of domestic life were distinct from the cults of death and burial. The example of Malta demonstrates that variation most emphatically. Elsewhere in the Mediterranean, the cults generally involved simple domestic rituals; little effort was invested in religious art or architecture. In Malta, however, the worship of corpulent images gradually blossomed into a consuming passion. That fixation may have been able to take root because conditions there enabled a closed, isolated, introverted society to develop.

Today the dry, rocky, hilly islands of Malta seem inhospitable to farming communities. Little soil or vegetation is present, and obtaining fresh water is a problem. Yet the geologic evidence suggests that between 5,000 and 7,000 years ago, a far more inviting scene greeted the early inhabitants. Those people probably cleared the fragile landscape of its natural vegetation fairly rapidly. Thereafter, severe soil erosion gradually robbed the islands of their productivity. The resulting environmental fragility may have caused agricultural yields to be unpredictable. That stress may well have shaped the strange and often extreme society that one finds portrayed in the archaeological record of ancient Malta.

The prehistoric archaeology of the Maltese islands is famed for its many huge stone temples. The number of them is staggering: some 20 groups of temples dot the islands, most containing two or three individual massive structures. Radiocarbon dating has indicated that they developed over roughly a millennium, from approximately 3500 to 2500 B.C. Because of their prominence in the landscape of Malta and Gozo, the two largest and most populous of the islands, the temples were always obvious targets for enthusiastic archaeological investigations, particularly during the 19th century. Those early workers cleared the rubble and

ISLANDS OF MALTA (*above*) are dotted with numerous groups of large stone temples. One noteworthy burial site, the hypogeum of Hal Saflieni (*below*), was discovered in the early part of this century. The authors are studying another burial site within the Brochtorff Circle.

other deposits from the temples long before scientific archaeology had developed. Little effort was made to specify the exact positions of the unearthed artifacts; in particular, the contexts of the cult idols were rarely recorded. Not much can be done now with that incomplete evidence, other than to appreciate the sculptors' high level of skill.

Although mostly stripped of its cult images and other decoration, the architecture of the Maltese temples still survives. The design of the temples is regular: each consists of a curved stone façade overlooking an open forecourt. The façade usually has a formal entrance, marked by enormous carved stones and a capstone, that leads to a central corridor. Lobe-shaped apses open onto this corridor at either side and ahead, as in a cloverleaf. The apses often had stone altars (which were frequently carved with spiral or animal designs), carefully plastered floors and walls and other decorations painted with red ocher, a pigment probably imported from Sicily. They also feature tie-holes, which in some cases were perhaps for fastening animals to the walls, and holes in the ground that were evidently for draining liquids. In many instances, substantial quantities of animal bones, particularly those of sheep and goats, were found together with drinking vessels and sharp flint knives. All these details suggest that sacrifices and feasting may have played an important part in the rituals performed in the temples.

Some information about the layout of the furnishings survived in the temples of Tarxien, which were excavated between 1915 and 1919. The lower half of an enormous statue of a "fat lady" was found in the temple precinct. Next to it is an altar within which the remains of food were found. The altar faced the carved figures of animals that may have represented sacrifices. Deeper within the recesses of the temple, excavators found the images of people who may have been priests, caches of precious pendants and even architectural models of the temples themselves.

The discovery in 1902 of the hypogeum, or subterranean burial chamber, at Hal Saflieni added another dimension to the cults of early Malta. Construction workers stumbled across this remarkable site while excavating cellars and foundations for new buildings in the surrounding town of Pawla. Before any skilled archaeologist was called to the scene, most of the chambers were emptied without documenting their contents; the rich assemblage of human remains and grave goods they must have contained probably ended up as fertilizer in nearby fields. A proper study of the hypogeum was finally conducted a few years later by Themistocles Zammit, the curator of the National Museum of Malta and the father of Maltese prehistory. He attempted to salvage what information he could from the near-empty chambers cut in the rock.

Zammit estimated that a fantastic number of individuals—between 6,000 and 7,000—had been buried in the 32 chambers of the hypogeum complex. They had been interred along with grave gifts of pots, obsidian and flint tools, jewelry consisting of beads and stone pendants, and clay and stone figures of obese people and animals. One of the most striking figures is the Sleeping Lady of the Hypogeum. This statuette shows a rotund female lying on her side on an elaborate woven bed. She is clothed in gathered skirts, and her hair is dressed in a small neat bun.

The various passages and chambers of the site strongly resembled the temples aboveground, with upright stone

blocks spanned by lintels, steps, hinge holes for barriers and perhaps painted decorations. Nevertheless, the primary function of the hypogeum was clearly for burial, as the thousands of bones attest. Yet it may have been more than simply a huge tomb. Its elaborately carved form, so similar in design to the temples, hints that it was also a temple for the dead, central to the rituals of death, burial and the afterlife.

The great number of figurines from both the temples and the ornate burial hypogeum of Hal Saflieni have fueled ideas (some plausible, some fantastic) about the supposed fertility cults and rituals of Malta. Some archaeologists have hypothesized that Maltese society may have been a powerful matriarchy dominated by priestesses, female leaders and mother goddesses. Those theories were always based on an implicit faith in the meaning of the artifacts—a faith as devout, in its way, as the prehistoric religion itself but lacking much scientific foundation.

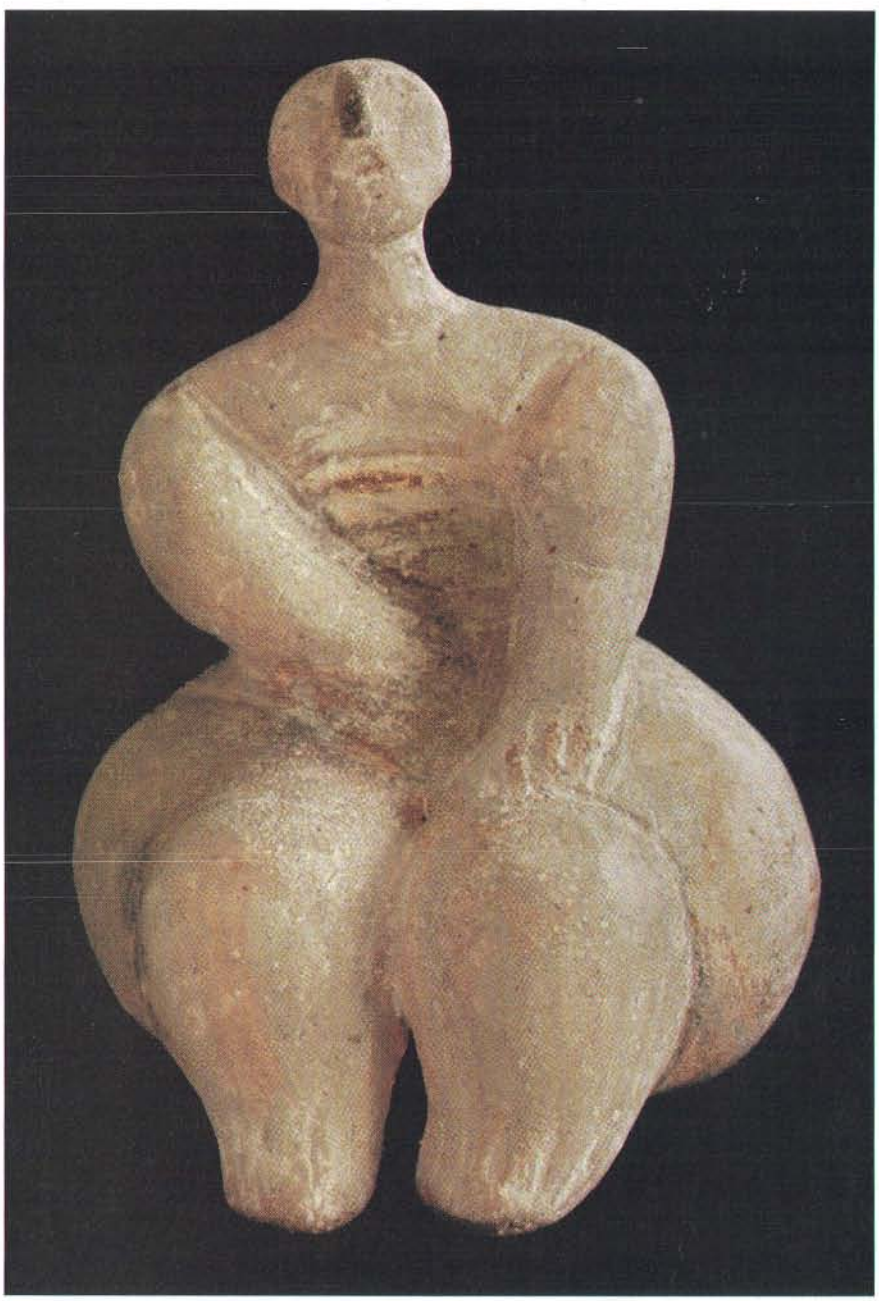
During the past five years, a new excavation at the site of the Brochtorff Circle on Gozo has uncovered important evidence about the prehistoric rituals of death. The Brochtorff Circle, a megalithic enclosure on the summit of the Xaghra plateau, was first discovered in the 1820s by Otto Bayer, the lieutenant governor of Gozo. Vague historical records suggest that a typically haphazard treasure hunt at the site followed, from which no findings or documentation survived. Those efforts obliterated all surface traces of the structure. Fortunately, though, a roving Maltese artist, Charles Brochtorff, made several sketches of the work while it was in progress. His accurate, detailed watercolors and engravings show a site that consists of a stone wall and entrance that encircle a huge rough hole at the center; several megaliths also stand within the enclosure. In one drawing, a man is shown climbing from the hole, holding an object shaped like a human skull.

That series of pictures was the only clue left to suggest that an archaeological site was located on the plateau. It served as a starting point for our team, which set out to rediscover whatever remained underneath the flat field. Using the most up-to-date scientific techniques, such as ground-penetrating radar, we conducted topographic and geophysical surveys of the area to assess the nature of the buried rock. In 1987 we succeeded in once again locating the Bayer excavation within a circle that had been found 20 years earlier.

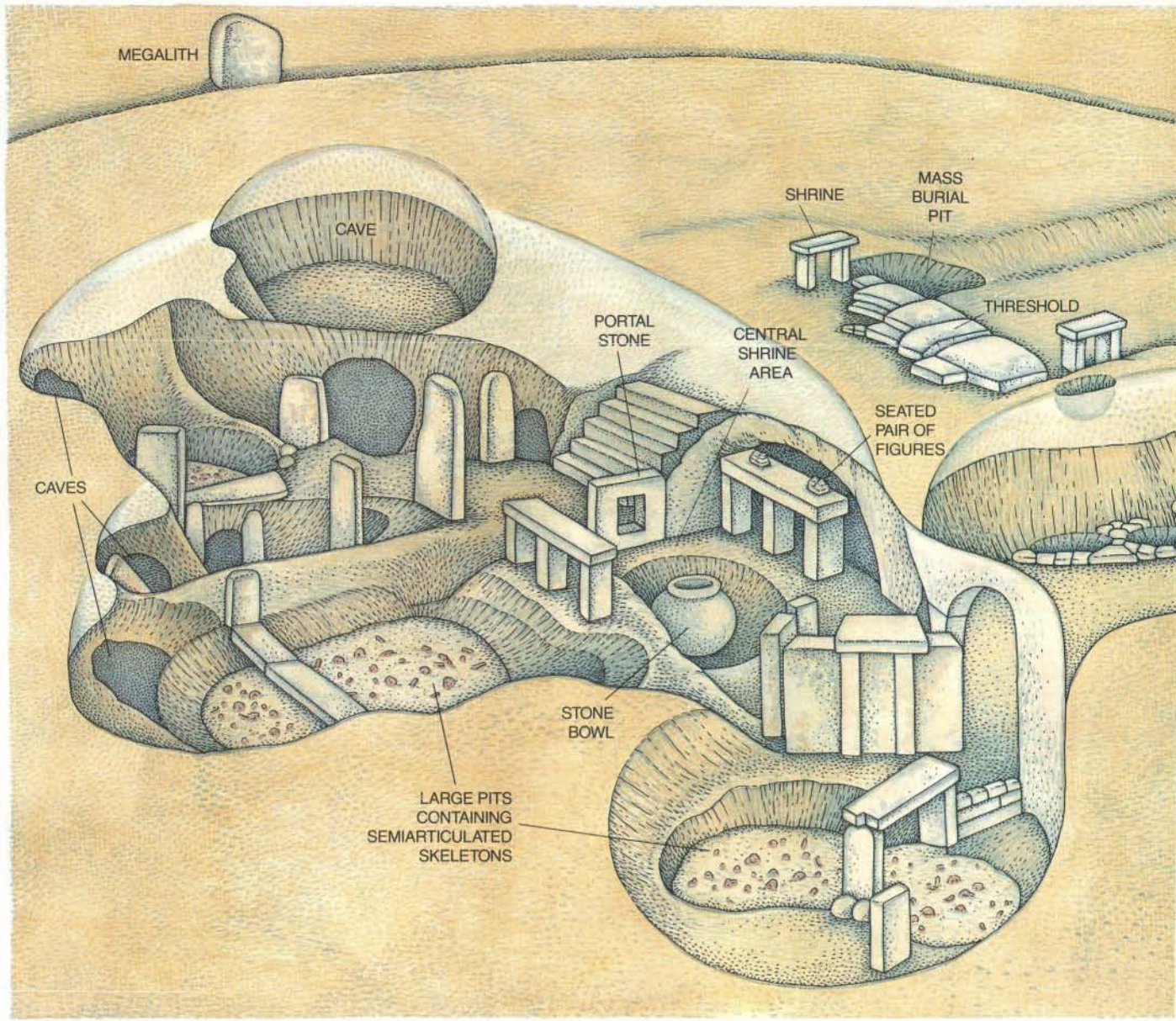
Since then, months of hard reexcavation have been spent at the site. Over an area of about a quarter acre, we needed to remove not only the 19th-century backfill but also the rubble from cave collapses that had filled several deep natural cavities to a depth of more than four meters. By the end of five work seasons, the true nature of the site was clear, and the rich array of recovered artifacts and human remains testified to its importance.

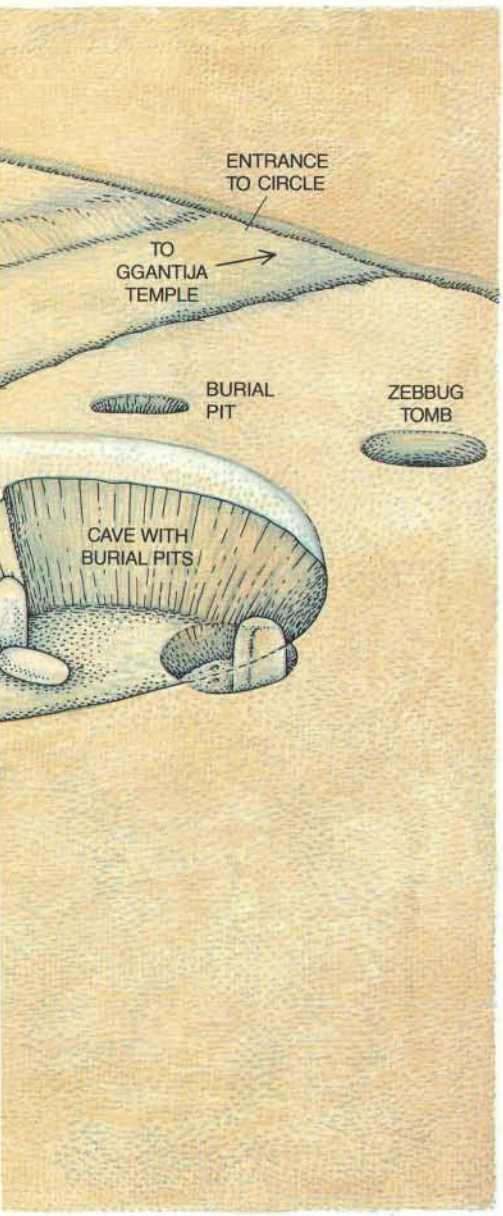
After the previous depredations at the site, we wanted to ensure that it was reexcavated with all the care and precision available to late 20th-century science. We therefore recorded and photographed every item at the base level of the caves in situ from several directions for a three-dimensional record of its position and appearance. Samples were taken for dating and also for studies of the local environment and subtle stratigraphy of the site. Paleoanthropological methods helped us to reconstruct a profile of the buried human population. We kept scrupulous computer records.

Unlike the great hypogeum of Hal



"FAT LADY" figurines representing mother goddesses were made by many early Mediterranean cultures, but those from Malta are the most elaborate. Not all the human figures from Malta are clearly female, however, which suggests that the ancient religion there involved much more than just the worship of human and agricultural fertility.


MEGALITH
CAVE
SHRINE
MASS BURIAL PIT
THRESHOLD
PORTAL STONE
CENTRAL SHRINE AREA
SEATED PAIR OF FIGURES
CAVES
STONE BOWL
LARGE PITS CONTAINING SEMIARTICULATED SKELETONS



Underground Burial Chambers

Brochtorff Circle marks a cave complex that the inhabitants of Gozo used for burials between 4000 and 2500 B.C. Treasure hunters found the site and then obliterated it in the 19th century, but in 1987 the authors and their colleagues found it again and re-excavated it. An aerial photograph (*far left*) shows the site as it appears today. The drawing (*above*) shows a partial reconstruction of the burial complex based on the most recent work. Thousands of human remains, many still adorned with ceremonial red ocher pigment, are clearly identifiable within certain pits in the cave floor (*near left*).

Saflieni on Malta, which consists mainly of artificial carved chambers, the Brochtorff site on Gozo is fundamentally a series of natural caves with numerous interconnecting chambers. Erosion and perhaps earthquakes have cracked the thin rocky roof of the caves, resulting in several meters of rockfall and jumbled archaeological deposits. The caves were crumbling even 5,000 years ago. The prehistoric community, which by that time had already been using the caves for the burial of the dead for perhaps 1,000 years, began to insert carved stone supports under the cave roof in a vain attempt to control the collapse.

The burial complex at the Brochtorff site was in use for about 1,500 years, a period spanning several stages in the evolution of Maltese religion and society. In the early Zebbug period between 4000 and 3500 B.C., burial rituals were simple. The dead were placed in collective chambers that were either in caves or in tombs cut into the rock. Each chamber may have held the members from a single family or lineage group. One such tomb was found inside the circle in 1988. The burial rites evidently included the progressive removal of bones from earlier burials to allow space for later ones; the large removed bones may have been dumped in other parts of the caves.

A variety of gifts were interred with the dead: pottery, bone and stone beads and pendants, stone axes made of metamorphic rocks, flint and obsidian blades, shell pendants, and shell and bead necklaces. The bone pendants often have budlike appendages suggestive of arms and heads. Red ocher was spread lavishly over the grave goods and also over the dry white bones of the dead (perhaps in a symbolic attempt to restore them to life). At the entrance to one of the chambers stood a small upright monolith, a so-called menhir, bearing a crudely carved face that guarded the doorway.

The later burials, which were contemporary with the great Tarxien period of temple building, were different. The emphasis on small family groups appears to have been supplanted by a more ritualized and elaborate cult of the dead. Part of the evidence for that conclusion comes from the megalithic construction of the Brochtorff Circle itself. The builders enclosed the opening to the cave with a wall and oriented its entrance eastward through the massive upright stones. In so doing, they integrated the entire site with the Ggantija temple, 300 meters away and on a lower terrace of the plateau.

Inside the caves the Tarxien builders leveled the earlier burials to provide a fresh (albeit bone-riddled) surface for the installation of stone monuments. The niches and smaller caverns were subdivided with pairs of upright stones and rough walls, which created additional, enclosed places for burials. At the center of the main cavern, the Maltese builders set up megalithic slabs in a semicircle, at the heart of which was a huge carved stone bowl. The stonework surrounding this bowl was elegant, and there is evidence that some of it included animal figures and pitted patterns. The builders did not apply red ocher as liberally as their predecessors did, and they painted only a few of the nearby slabs.

Bodies were buried in the compartments around this central shrine. One noteworthy burial site was a natural cavity in the cave floor where hundreds of bodies were laid to rest. At first sight, the remains seemed incomplete and in confusion. Our further work has shown, however, that the bones from many bodies had been carefully sorted and stacked by type: skulls in one place, femurs in another and so on. This pattern suggests that as part of the burial ritual, old bodies being removed from compartments were disarticulated.

The thousands of human bones, which probably represent hundreds if not thousands of individuals, are now being studied. The early results paint the ancient Maltese as a typically Mediterranean people—stockily built and of medium height. They show some distinctive characteristics, such as a digastric fossa, a well-formed groove on both sides of the skull that is found in some other populations. Their health was apparently very good, with few dental problems or other detectable illnesses. The same anthropological features are present from the earliest Zebbug people to the late Tarxien population, which evinces little or no change in the genetic makeup of the early Maltese community. The changes in their customs and cults were therefore probably not the result of foreign immigration. Scientific studies of the bones will continue for the next few years, providing one of the first and possibly the biggest samples of research on an early Mediterranean population ever undertaken.

The only grave goods with these Tarxien people (which have been dated by the radiocarbon method to around 2800 B.C.) were small, carefully modeled ceramic statuettes of obese human figures. These figurines are almost certainly female because of the distinctive accumulations of fat on the buttocks. Their discovery in that location was highly significant: it marked the first secure association of "fat ladies" with burial sites instead of shrines or temple altars.

On the ground surface, at the monumental entrance leading down into the caverns, another pit was also filled with human remains. Among them were many males whose body parts had been rearranged after being taken from some other burial place. Almost no grave gifts accompanied the bones. Small altars at either end of the megalithic pavement beside the burial pit may have been used for preliminary sacrifices and obeisances before the priest and the assembled mourning community ventured down into the foul, reeking caves of the dead.

The most exciting discoveries from the Brochtorff site, aside from the human remains themselves, are small stone sculptures that have changed our views about the role of art in the ancient local religion. The prehistoric Maltese of the Tarxien period seem to have invested most of their artisanship and craft into cult objects that were more than mere grave gifts. For example, a ceramic strainer and a unique stone sculpture were unearthed from near the stone bowl in the megalithic shrine. The strainer was probably meant to be used with the bowl, perhaps for straining out unwanted objects or for sprinkling liquids onto bodies.

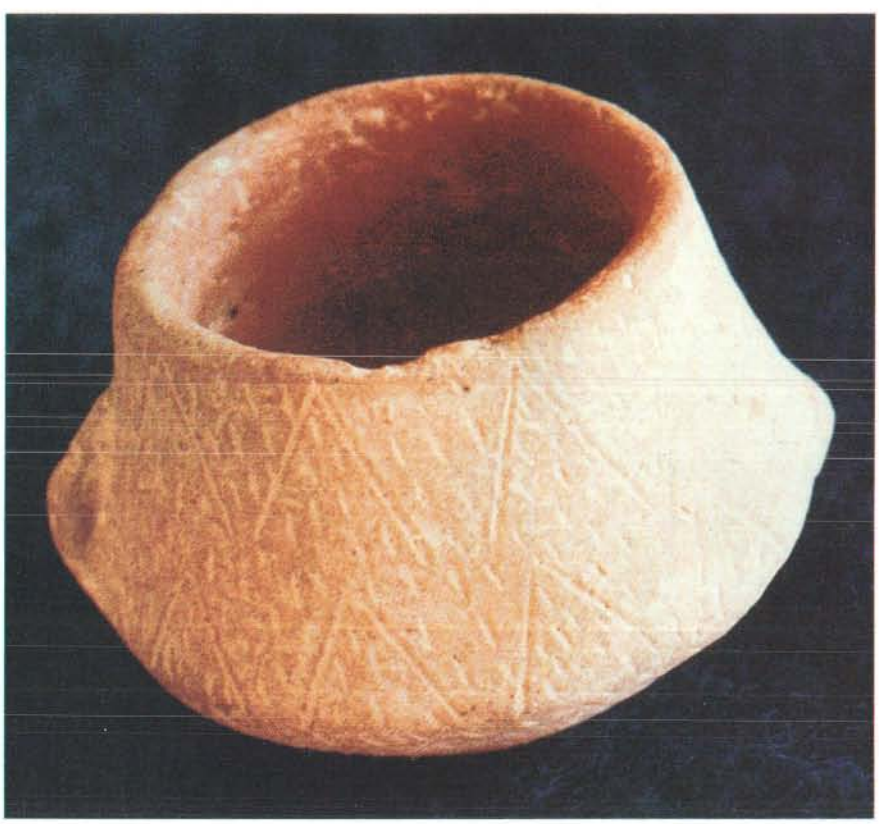
The sculpture shows a beautifully carved and painted pair of obese figures. They are seated on an intricately carved bed, daubed with red ocher, that shows woven struts on the underside and curvilinear designs on the upper. The fat figures are not explicitly male or female. They wear the familiar pleated skirts, painted black, of the finest Maltese cult figures. The head of one figure sports a haircut that includes a pigtail at the back. The other's head is missing, and we can only hope to find it in future seasons of excavation. Both figures hold objects on their laps: one a tiny dressed person (who may be a baby), the other a cup.

Aside from the sculpture's fine craftsmanship, it is astonishing because the portrayal of several humans together is almost unknown from that period in Europe: even individual figures, other than the "fat ladies," are uncommon. A few artifacts with features that are reminiscent of this sculpture have been found elsewhere in ancient Malta, such as the fragments of carved beds and the terra-cotta Sleeping Lady of the Hypogeum. Nevertheless, this discovery is one of the earliest and most thought-provoking groups of sculpture from European prehistory.

The other major find was a cache of nine carved stone idols, which were also closely associated with the stone bowl in the central shrine. The objects must originally have been wrapped tightly in a bag or box: when they were discovered in 1991, they were all lying one above the other, having fallen from the structures surrounding the bowl. Six of the objects represent human figures: flat, triangular shapes attached to carvings of human heads. The six range from poorly detailed rough-outs to skillfully executed cult idols. Two of the most detailed figures have pleated skirts and belts, and one wears an elaborate crested circlet, seemingly of metal, around its head. The faces of both these figures show eyes and lips and well-defined noses. A third figure is simpler and has no costume other than an exquisitely sculpted cowl headdress. Two more have plain bodies and bobbed hair. The last of the six is a crude rough-out that shows only the lines that the finished sculpture was to follow.

The three other idols of the nine are small and individual. One has a pig's head, the second a well-carved human head on a phallus-shaped pedestal and the third a head supported by two legs. Along with these extraordinary objects was a miniature Tarxien pot filled with ocher, perhaps for smearing on idols.

No parallels for any of these strange objects have ever been found elsewhere in Malta or the central Mediterranean. Even so, our knowledge of the context in which they appear is informative. Whereas the figures associated with the dead in their burial chambers are "fat ladies," those from the central shrine are much more complex. One cannot find an emphasis on images of female fertility in the shrine. Indeed, where the imagery is interpretable, it seems to be male and animal. The context of their discovery suggests that the shrine objects were the paraphernalia employed by the ritual specialists or priests and that their symbolism was meant to evoke much more than just a mother goddess.



SMALL CERAMIC POT was used to hold red ocher, a pigment daubed on ritual figures and human bones during Maltese burial rites.

Unprecedented discoveries at the Brochtorff Circle have encouraged us to reconsider the whole basis of ancient cults and religions in prehistoric Malta and Gozo. As the old ideas had supposed, the worship of fertility may well have been a component of the prehistoric religion. But the recent findings argue that it would be a mistake to concentrate exclusively on any one facet or historical period: the prehistoric religion of Malta was not only an infatuation with fat females.

During the Zebbug period between 4000 and 3500 B.C., the cult focused on the provision of caves and underground tombs as burial places. Accurate depictions of people do not seem to have played a part in the local rituals: the

SMALL STONE IDOLS were probably used by priests or other specialists in burial rituals at the Brochtorff Circle during the Tarxien period. The three on the left representing human figures show very different levels of detail and artistic execution. The other three, which invoke animal and phallic imagery, are more fanciful and individualized.

closest representations of human forms in the tombs are the very crude faces on the menhirs and the curious bone pendants with budlike arms and heads. Red ocher was the predominant decoration. Exotic axes of green stones and other objects made of flint and obsidian were also used as grave goods. In many ways, the early ritual developments appear to have paralleled similar trends in Sicily, where rock-cut tombs and simple collective burial rites were developing at the same time. The Maltese islands during this early period were still relatively fruitful and may not have been overpopulated.

But by half a millennium later, Malta seems to have been shaken by major changes. The erosion of the soil and other signs of environmental degradation may have become apparent; in this environment, population levels almost certainly began to pose problems. Artifacts from that period—the obese human and animal figurines and the phallic symbols carved in stone or bone and modeled in clay—point to the idea that the people had an obsession with the living world and its successful propagation. Malta seems to have become an island world under powerful economic and environmental stress, where the communities were struggling to maintain their former standards of living and to feed the population. Yet fewer materials were imported into the islands during this time of crisis than in the more fruitful era. The prehistoric Maltese society seems to have let a fixation on sculpture and art replace contact with the world beyond the islands' rocky coasts.

That debilitating fixation may explain why the temples are so numerous on so small a group of islands. Some scholars have theorized that they were built by perhaps half a dozen rival clans or tribes, each competing for land and water. The colossal size of the temples, and the later architectural additions that made them even more prominent, could have been inspired by such a competitive spirit. Religious and cult influence and social control over the population may also have been influential.

Cult activities seem to have reached a feverish pitch in the final phases of the Tarxien period around 2500 B.C. The society was becoming increasingly dominated by a religious hierarchy in which cult specialists or priests controlled much of the industry of the people. Vast amounts of human time and energy were invested in temple building, artistic endeavors and ritual feasts. The dead were honored within cults and linked to animals and human obesity. The people seem to have expended relatively little effort on the building of villages or domestic structures, on terracing or on farming methods. The obsession with the cults of the temples seems to have been complete.

Such obsessions are dangerous, and so it proved to be on ancient Malta. By about 2500 B.C. the community of the temple builders had ceased to build and perhaps even to use the monumental burial sites prepared by earlier generations. By 2000 B.C. the entire culture had disappeared and been replaced by very different religious practices that favored cremation burials. The burial hypogea, the cult of the "fat ladies" and the other symbols of the living and the dead were completely abandoned.

The prehistoric religion of Malta might appear to be a failed experiment in the Mediterranean laboratory. Like many failures, however, it tells us more than a success might have. The extreme religious fervor of ancient Malta shows one of the possible results when societies are placed under severe pressures. Further careful excavations and reconstructions on Malta and at other Mediterranean sites should extend our understanding of the complexities and diversity of prehistoric society. To that end, the excavations at the Brochtorff Circle continue.

FURTHER READING

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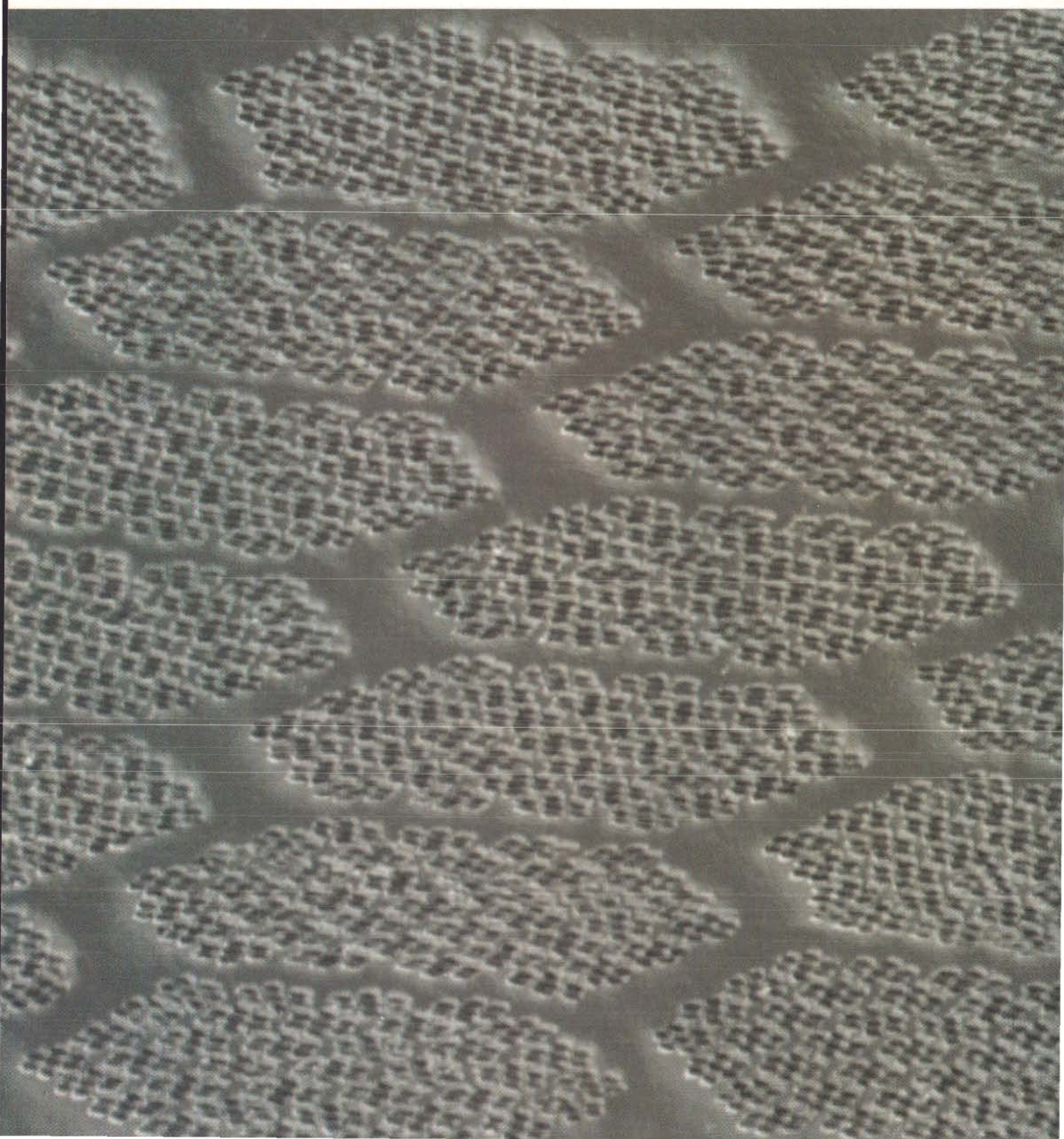
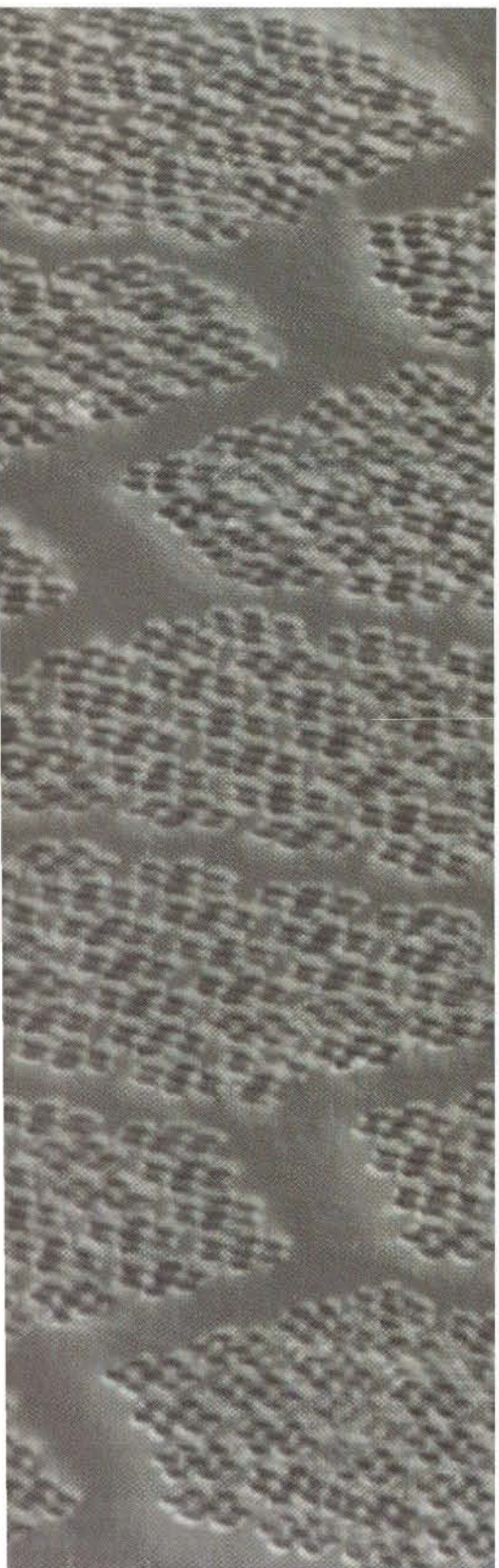
Current Events

by Philip Yam, *staff writer*



Now that the blizzard of hype has stopped, workers are gradually realizing the promise of high-temperature superconductors



Over a smoky bath of liquid nitrogen hovers a disk-shaped magnet. Wei-Kan Chu, the deputy director for research at the Texas Center for Superconductivity at the University of Houston (TCSUH), suggests knocking the floating magnet about. Such demonstrations have become a customary part of a visitor's tour at many laboratories that harbor work in superconductivity, but they are, like a rainbow, still impressive. As expected, the suspended disk resists all attempts to force it up, down or sideways. It can, however, be set spinning, slowed only by friction with the air. The system is about the closest thing to a perfect ball bearing or flywheel.

Although the demonstration hasn't changed, the atmosphere in the world of high-temperature superconductivity has. Gone is the sound of hype, the White House pronouncements, the high-level conferences from which "foreign" researchers were pointedly excluded. Discussion in the field no longer swirls around national competitiveness, magnetically levitated trains (the putative offspring of the floating magnet) and super supercomputers. Today workers focus on incremental advances and modest applications—a strategy that may actually bring the millennial visions of the hypesters to reality faster than any crash program would have.

Discovered in the late 1980s, these ceramic compounds—yttrium-barium–copper oxide (YBCO for short, and pronounced "yibco") and its relatives, containing bismuth or thallium combined with copper oxide—promised to expand greatly the market for devices that exploit superconductivity. When cooled below a critical temperature, a superconductor not only transmits electricity without resistance but also wards off intruding magnetic fields. Conventional superconductors, made of metals and alloys, must be cooled to a brittle four degrees above absolute zero with liquid helium. They have seen limited applications because of the cost (about $4 a liter) and rapid boil-off of the liquid helium. The critical temperature of the ceramic superconductors exceeds 90 kelvins. A material could be cooled to a point below that temperature with liquid nitrogen, which boils at 77 kelvins. Liquid nitrogen costs as little as 10 cents a liter, making it cheaper than Kool-Aid. Equally important, liquid nitrogen lasts 60 times longer than liquid helium given the same heat load.

***HIGH-WIRE ACT:** a lateral cross section of a high-temperature superconducting wire is magnified 300 times. Made by American Superconductor, the wire consists of superconducting filaments, each four microns thick, packed into hexagonal patterns. This approach makes what would otherwise be a brittle wire bendable and able to resist cracks.*

The products available now are such specialized devices and components as magnetic field sensors for educational purposes, current leads in magnetic resonance imaging (MRI) systems and even a dipstick that measures levels of liquid nitrogen. Although hardly the kinds of applications that fire the imagination or revolutionize a society, these and other devices represent tangible victories in making the new superconductors a commercial success. "Progress to date has far exceeded realistic expectations," says Thomas R. Schneider of the Electric Power Research Institute (EPRI), the utility-funded organization headquartered in Palo Alto, Calif.

Schneider chooses his words deliberately, emphasizing "realistic." As he uses the term, realistic means prototypes, demonstrations, contracts and long-term goals. By that measure, progress has indeed been gratifying—and ahead of schedule, according to many workers. Investigators have demonstrated and are ready to produce components for microwave communications and military tracking. Wires are getting longer and are able to carry more current. Devices have been built from them that prove the technical feasibility of power applications. "I didn't expect to see anything real this century," remarks physicist John Clarke of the University of California at Berkeley. "The field has progressed much more quickly than I would have guessed." Adds Alan Lauder, director of Du Pont's superconductivity research: "I am perhaps more optimistic than I ever have been that this technology will develop into beneficial systems."

Against the Grain

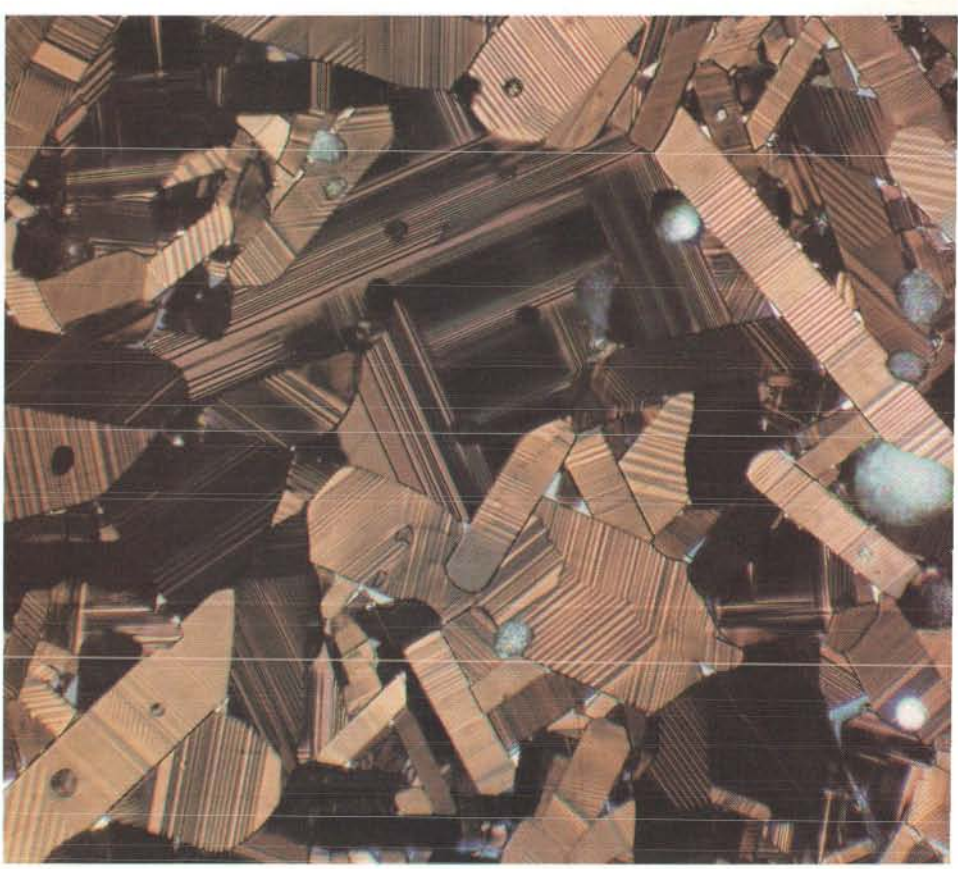
What makes the recent progress such a source of optimism is that the materials are inherently intractable. After all, they are ceramics. How does one fashion wires or circuits from a substance with the fragility of chalk? Just as challenging, the material can suffer from "weak links." High-temperature superconductors consist of grains. Electricity has no problem flowing within a grain, but sometimes it does have trouble getting from one grain to the next because the grains are not always properly coupled to one another. Large gaps can separate them, and any misalignment—even by a mere five degrees—inhibits the resistanceless flow. Weak links can limit by two orders of magnitude the amount of current carried.

An even more daunting challenge came from external magnetic fields. In many envisioned bulk applications, such as motors, transformers and levitation devices, the presence of a magnetic field is an integral part of the technology or, at least, an unavoidable byproduct of the system's operation. Whatever its provenance, a sufficiently strong external field can penetrate the superconductor in the form of discrete bundles of flux lines, or vortices. If the superconductor is cold enough, the vortices remain locked in place, forming a latticelike pattern. Current flows around them without much difficulty. But at warmer temperatures, the magnetic flux bundles begin to "creep." At sufficiently high temperatures, the vortex lattice "melts": the vortices move around in the material, blocking the flow of electricity [see "Resistance in High-Temperature Superconductors," by David J. Bishop, Peter L. Gammel and David A. Huse; SCIENTIFIC AMERICAN, February]. More distressingly, the melting transition for all the copper oxides lies below the temperature of liquid nitrogen.

The combination of weak links and vortex motion can severely hamper the flow of current in the new superconductors. Unless a way could be found to overcome the problems, there was little reason to replace existing low-temperature superconductors, which do not suffer from those difficulties. Such conventional superconductors, mostly niobium alloys, can carry more than 100 times the current ordinary copper can: 100,000 amperes per square centimeter in a high magnetic field of several teslas. (For comparison, the earth's magnetic field is only about 0.1 millitesla, and the field generated by MRI devices is less than two teslas.) Fundamental issues such as vortex motion are relevant to those seeking applications, says David J. Bishop of AT&T Bell Laboratories, one of the investigators who discovered the vortex phenomenon. "It makes what they are trying to do harder." It did—and does—indeed. By 1989, less than three years after their discovery, the high-temperature superconductors did not seem so super after all. Media reports suggested that the large-scale applications might remain a fantasy, and pessimism pervaded the field.

Filming the Ceramics

Like guerrillas confronting a superior force, some workers in the field decided to go around rather than through



DISORDERED GRAIN STRUCTURE of the superconductor YBCO causes the weak link problem. The poor alignment, as well as any impurities that might exist at grain boundaries, strongly hampers the flow of electric current moving from one grain to another.

the opposition. They knew that the problems of weak links and flux creep would severely challenge "bulk" applications—that is, in uses as wires for motors, coils and transmission lines. They also knew that the problems were much less daunting in so-called thin-film uses—specifically, in the area of electronics.

Instead of drawing flexible wires out of brittle material, electronics developers attempted to lay down micron-thin surfaces and etch circuit patterns on them. Weak links are not a serious issue, because the grains can line up with the substrate on which the film must be grown (the substrate acts as mechanical support and affects the direction of grain development). Furthermore, the entire sample is small, so relatively few grain boundaries exist that could impair current flow. Flux creep is not a problem, because electronic components are rarely used in an environment suffused by strong magnetic fields. Thin films of YBCO can conduct five million amperes of current per square centimeter at 77 kelvins.

Because they suffer less from weak links and magnetic flux, thin films were predicted to reach the market early as components in electronic devices. They would, experts said, be useful in cellular communications systems and in biomedical sensors. In such applications, they would be much smaller and would handle more information than existing elements could.

SUCCESS IN THIN FILMS enables John M. Rowell of Conductus to offer for purchase one of the few products made from the new superconductors: Mr. SQUID, a $1,995 magnetic field sensor.

Such experts were not the first to use a cloudy crystal ball. The manufacture of large thin films of good quality proved to be the prime barrier to electronic applications. "We were surprised to find out how difficult these materials are to work with," says John M. Rowell, the chief technical officer of Conductus, a Sunnyvale, Calif., start-up specializing in thin-film applications. "There was no knowledge base for the oxide materials." The superconducting properties depend heavily on crystal structure. During processing, insulating phases of the material often appear. Substrate choice was also a challenge. During the manufacture, "the substrate might get chewed up or go into the superconductor," says James H. Long of Superconductor Technologies Incorporated (STI) in Santa Barbara, Calif. Largely through trial and error, film makers have mastered their craft. They can create market-worthy films that are as much as a few inches in diameter.

The superconductor of choice for most film applications is YBCO. A YBCO film carries more current than do members of the bismuth family. The relatively small number of elements in YBCO makes the material simpler to produce than thallium-based films. Organizations producing thin films have settled primarily on two ways to deposit the superconductor: laser ablation and sputtering. In laser ablation, a pulsed excimer laser vaporizes bits of the superconductor, which then crystallize on the substrate. In sputtering, the superconductor is evaporated by a plasma onto a substrate.

Companies such as STI and Du Pont have recently delivered filters, resonators and delay lines that operate at microwave and radio frequencies. Although not the kind of devices to appear in the Sharper Image catalogue, such components are common elements in military instruments and communications systems. Devices made with superconducting materials provide better signal strength and allow more efficient signal processing while avoiding such drawbacks as large size and high electrical loss. For example, STI made a delay line used by the military to deconstruct for analysis signals from a target. The component measures less than four inches square, a major reduction from the 70 feet of stainless steel coaxial cable typically needed to provide similar performance, according to STI.

PLATELIKE GRAINS of the superconductor BSCCO overcome the problem of weak links. In a process called powder-in-tube, a combination of deformation and thermal processing aligns the grains, laying them flat on top of one another. Electricity proceeds unimpeded from one grain to the next.

Several companies have also created interconnects, resistanceless bridges linking one component to another. Interconnects could be useful in multichip modules. These dense packages of several computer chips constitute an alternative to ever finer patterns etched on silicon wafers.

For entrepreneurs seeking large-scale commercialization, the telecommunications industry is the obvious target. "The cellular market is enormous," says Ora E. Smith, president of Illinois Superconductor, which makes the dipstick for liquid nitrogen. Industry experts say cellular base stations already constitute a $5-billion-a-year business. One way to tap into this market is through filters, which base stations use to remove the extraneous radio-frequency noise that peppers the cellular environment. Filters made from superconducting materials would maintain the integrity of calls better than conventional filters do and would help each cell handle more channels. AT&T Bell Labs, Illinois Superconductor and other companies are working on such cellular filters. "We're hoping to have the filter on the market in 1994," Smith says.

Electronic Calamari

Demand for acute magnetic-sensing devices also constitutes an opportunity. A high-temperature superconductor can be configured as a SQUID (a superconducting quantum interference device). A SQUID is a loop of superconductor etched in silicon. The loop contains one or two links that are only weakly superconducting. The flow of electrons that tunnel through the link, called a Josephson junction, is extremely sensitive to magnetic fields. The change in the flow shows up as a measurable change in voltage across the junction. Making such devices embodies fabrication challenges that only now are just being met.

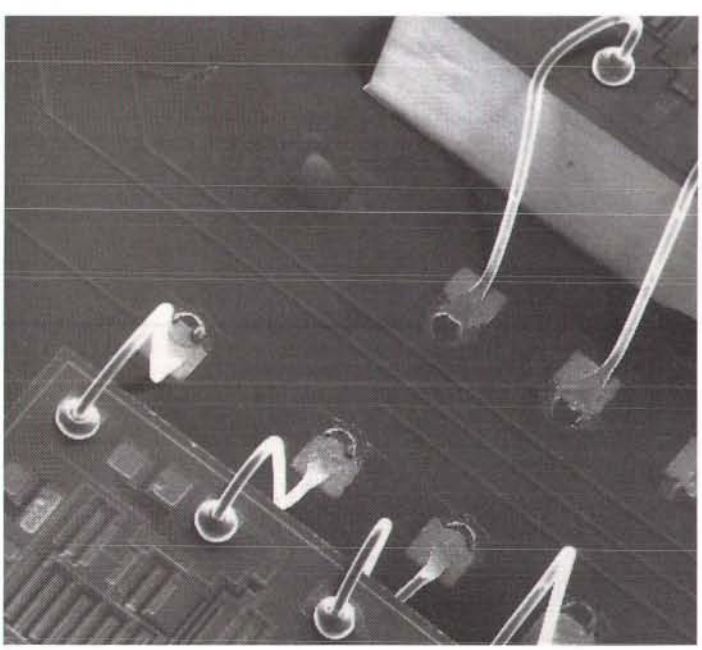
Conductus already markets a magnetometer called Mr. SQUID, designed primarily as an educational tool. Improved versions should enable engineers, at low cost, to discover defects without damaging or coming into contact with a mechanical structure. That is because defects in metallic structures produce magnetic "signatures" that SQUIDs can detect. Energy companies might also find SQUIDs useful. Because rock conducts electricity weakly and oil is an insulator, geologists could rely on the devices to prospect for petroleum. But the biggest prize for small companies is the clinical market. "The Holy Grail of the SQUID business is biomagnetic measurement," Clarke points out. SQUIDs made with copper oxides should soon be sensitive enough to detect electromagnetic signals from the heart and brain, thus providing a noninvasive diagnostic tool.

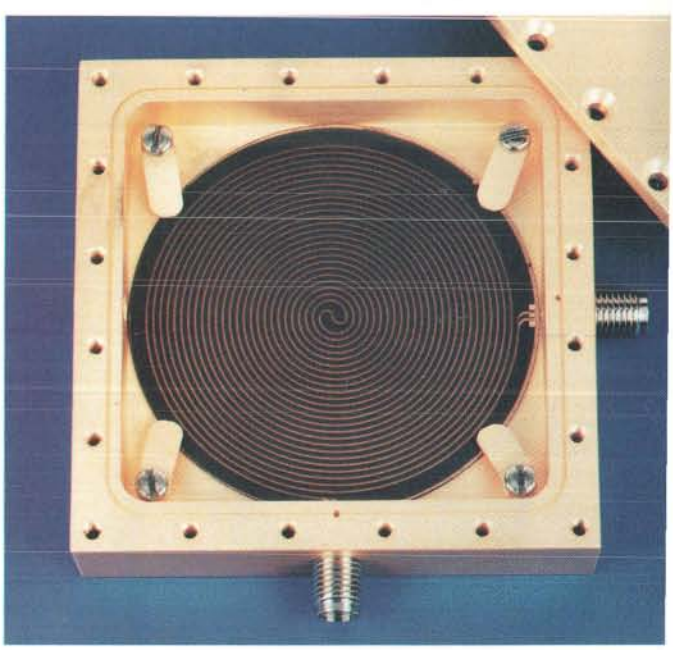
The new superconductors may also improve MRI systems or make them less expensive. Configured as a "pickup coil," a ceramic superconductor could improve the signal-to-noise ratio of many instruments without resorting to costlier large magnets.

What about superconducting computers? There has been some progress, but digital electronics products are not likely to emerge until past the turn of the century. Researchers have designed electronic switches from Josephson junctions, which consume only a few microwatts to turn on and off in a few trillionths of a second. The junctions not only consume one thousandth the power of semiconductor devices but are also 10 times faster. Workers have also demonstrated so-called flux flow transistors as alternatives to Josephson junctions. The principle turns a major shortcoming of the materials—the movement of magnetic vortices—into a benefit. The motion of flux lines generates voltages that can be modulated by a gate to perform logic functions.

A third kind of switch derives from a basic element in modern electronics: the field-effect transistor. In such transistors, an external electric field changes the number of charge carriers in a semiconductor. Only a few workers, however, have demonstrated superconducting field-effect transistors (suFETs). They include Xiaoxing Xi of the National Institute of Standards and Technology and his colleagues at the University of Maryland.

Whereas microwave and SQUIDs are the nearest in terms of substantive markets, "it will be 10 years before you see digital implementation," Du Pont's Lauder predicts. Manufacturing high-quality multilayer films and patterning them reproducibly and cheaply has proved difficult. "While the digital demonstrations are encouraging, there are some issues about circuit architecture that need to be clarified," says Richard W. Ralston, the principal director of the Consortium for Superconducting Electronics (CSE). Founded in 1990 during the height of the concern about American competitiveness, the consortium pairs two traditional rivals, IBM and





AT&T, with the Massachusetts Institute of Technology, the M.I.T. Lincoln Laboratory and several small companies and other academic institutions to speed commercialization of the new materials.

Stringing It Along

Success with thin films has put several markets for the copper oxide superconductors within reach. For their part, workers who attempt to master bulk materials have at least begun to enjoy some technical success. One measure of progress is in the production of wires—making them longer, more flexible and better able to resist the incursion of flux lines.

Amid the unremitting hum of machinery, punctuated by shrieking loudspeaker pagings, technicians are busy checking long lengths of wire. In its new facility, American Superconductor Corporation in Westborough, Mass., has been gradually coaxing the ceramic superconductor into wire. The joke, believed to have originated in the thin-film community, is that the move to this much bigger facility was necessary because the wire did not bend. But a tour of the pilot manufacturing line quickly dispels that bit of cynicism.

Since its founding in April 1987, American Superconductor has been competing vigorously with Sumitomo Electric Industries in Japan and Intermagnetics General in Guilderland, N.Y., to produce flexible, longer and better superconducting wire. The Massachusetts company has pulled ahead: it can regularly spin out 300 meters of ductile wire that can carry more than 10,000 amperes per square centimeter in zero applied field at 77 kelvins. The company plans to break the kilometer mark in April 1994. Such an advance would qualify the copper oxide wires for consideration as transmission lines. Transmission lines must sustain power densities of at least 20,000 amperes per square centimeter at kilometer lengths.

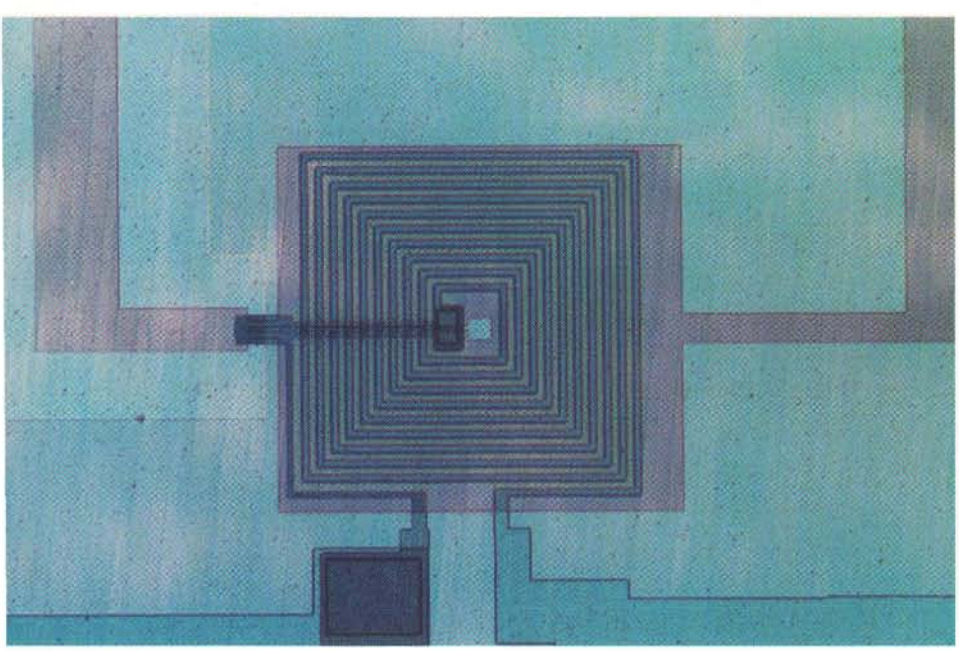
FOR SALE? Richard W. Ralston, principal director of the Consortium for Superconducting Electronics, holds a prototype filter for satellite communications and a disk of YBCO film ready to be patterned into a circuit.

This past year American Superconductor fashioned its wires into coils for Reliance Electric in Cleveland, Ohio, which built a two-horsepower motor—strong enough to power the cooling fan in a desktop computer. Even more recently, it constructed a sonar device for the U.S. Navy. "Essentially, it's a big woofer," explains Gregory J. Yurek, the president of American Superconductor. The device is meant to give coverage in a frequency range previously inaccessible to conventional sonar.

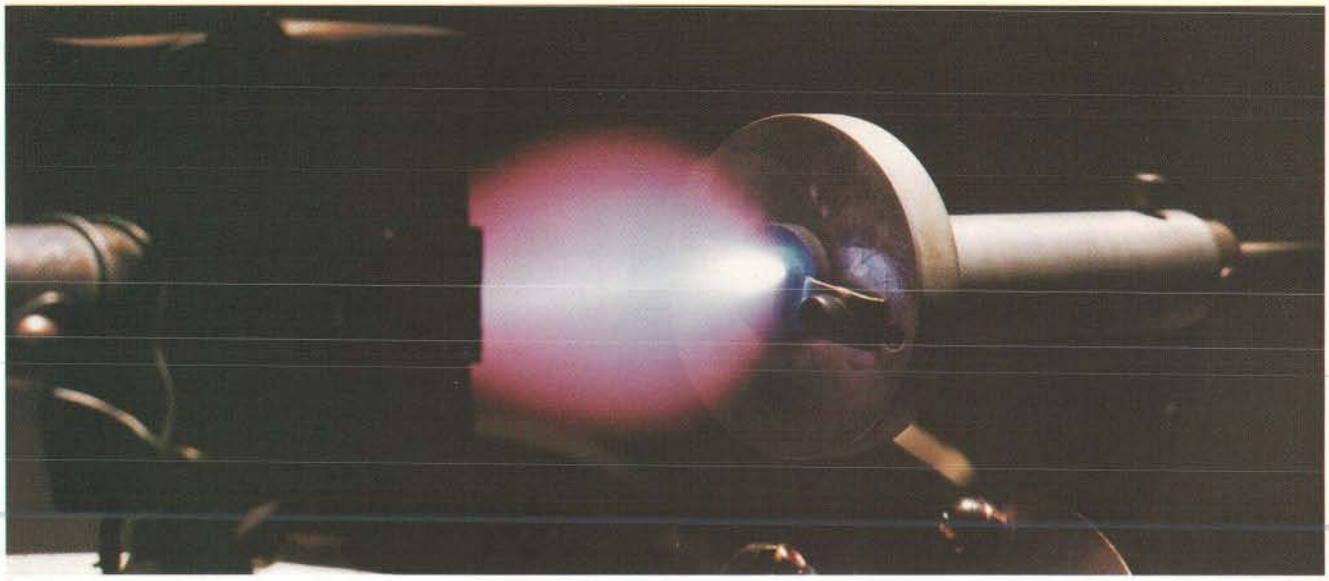
The long lengths of flexible wires, the coils and the big woofer stand as remarkable accomplishments in light of weak links and magnetic vortices. "Fortunately, the scientists and engineers did not give up on the materials," Yurek observes. The problem of weak links was solved by the discovery of a bismuth-strontium-calcium-copper oxide, or BSCCO ("bisco"), compound. "The breakthrough came with the bismuth material, which allows us to align the grains so that current flows from one grain to the next," says Roger B. Poeppel of Argonne National Laboratory.

Like other companies and laboratories, American Superconductor creates BSCCO wire using the powder-in-the-tube method, a technique first developed in 1989 by Vacuumschmelze in Germany. A silver tube is packed with a precursor powder. The tube is deformed—through extrusion, rolling or pressing—into a wire (or a tape if the cross section is rectangular). Then the tube is heated to transform the precursor powder into BSCCO. The resulting wire is protected by the silver sheath, which also serves as an alternative pathway for current in the event that the superconductivity is lost. The wires, too, are bendable, because they actually consist of thousands of even finer wires. Alexis P. Malozemoff, the company's chief technical officer, explains: "Without the multifilamentary structure, these wires would be brittle structures and would present a real problem in their handling, durability and their ability to perform over time."

To pack the filaments in, American Superconductor makes one wire, bundles it with other wires, then bakes the assemblage. Because composites are inherently stronger than a single pure



ELECTRONIC DEVICES made with copper oxides include 20-micron-wide interconnects (*the four etched lines that lie diagonally across the image*), which run between gold-wire bonds connected to silicon chips (*left*); a delay line, used in microwave electronic systems to slow signals down a few nanoseconds (*center*); and a SQUID magnetometer (*right*), an integrated circuit that consists of a stack of superconducting and insulating layers. The SQUID itself is the light purple layer; the multiple turns on the SQUID help to amplify the magnetic field to be detected.



LASER ABLATION lays down thin films of superconductor. The luminous plume appears when an ultraviolet laser pulse (*not visible*) strikes a sample of the superconductor mounted on a target holder (*device at right, where plume emerges*). The pulse vaporizes some of the sample, which collects on a heated substrate (*in housing at left of plume*).

material, the cable resists strain and cracking, even after many cycles of cooling and warming.

Although such multifilamentary BSCCO wires have surmounted the difficulties of weak links and flexibility, the motion of magnetic vortices continues to cause trouble. The BSCCO formulation used in wires, which becomes superconducting at 110 kelvins, has to be cooled to about 25 kelvins to keep the magnetic vortices fixed. In applications requiring exposure to high magnetic fields, BSCCO wires must be chilled with high-performance refrigerators called cryocoolers, which are more expensive than liquid nitrogen.

Because BSCCO pins magnetic vortices so poorly, researchers have been exploring ways to create wires out of thallium-barium-calcium-copper oxide, or TBCCO ("tibco"). TBCCO materials are superior in this respect. In TBCCO, flux can be frozen at temperatures near those at which nitrogen becomes liquid, Poeppel says. Furthermore, the transition temperatures of TBCCO formulations are among the highest of the copper oxides. Two varieties become superconducting above 120 kelvins.

But unlike BSCCO, whose grains are platelike and hence can lie flat, TBCCO consists of grains that are roughly spherical. This geometry does not lend itself to the manufacturing techniques that produce wires of BSCCO. An attempt to enclose a powder of TBCCO in a tube would resemble wrapping aluminum foil around rocks, explains John A. DeLuca of the General Electric Research and Development Center in Schenectady, N.Y. "The little rocks would come right through the silver tubing."

Instead many researchers are borrowing a method from thin-film workers: they deposit TBCCO onto a substrate. Although not yet commercially practical, this approach produces materials that successfully pin magnetic flux and maintain a high current density.

One such approach is emerging from a collaboration between DeLuca's group and workers at Oak Ridge National Laboratory. A solution containing barium, calcium, copper and oxygen is sprayed on an inert substrate known as yttria-stabilized zirconia. The sample is then heated in a thallium-rich vapor to form a film three to four microns thick. This "thick film" approach produces colonies of aligned grains. In zero field at 77 kelvins, the films carried up to 104,000 amperes per square centimeter. The film has supported a current density of more than 10,000 amperes per square centimeter in a magnetic field of two teslas.

Laser ablation is also being studied as a method to deposit TBCCO. Richard E. Russo and his colleagues at Lawrence Berkeley Laboratory have managed to create the highest critical current density in bulk thallium samples to date: 600,000 amperes per square centimeter at 77 kelvins.

Fixing Fickle Fluxes

But to get the most out of the superconductors, researchers may ultimately have to be able to introduce magnetic flux pins deliberately, just as they do for the low-temperature materials. Flux pins are defects in a solid that have a particular size and shape. Magnetic vortices tend to settle on those defects, just as marbles will lodge in depressions on a surface. The best pins are those that match the size of the so-called coherence length of the substance. The coherence length refers to the separation between superconducting electrons. In a high-temperature superconductor the coherence length is extremely short, typically one to three nanometers—roughly 30 times the diameter of a hydrogen atom. In low-temperature superconductors, the coherence length is much longer, about five to 30 nanometers.

Investigations pursue several different approaches. The most common is particle irradiation: bombarding the sample with energetic ions, neutrons or electrons. Such shotgun techniques create pinning sites by slightly displacing the atoms in the material. Irradiation with heavy ions can also produce columnar defects that act as sleeves to hold the vortices.

The technique has a severe limitation. To use it, one must have a particle accelerator. "We are getting an understanding of what is required, and the national labs are working with industry to come up with practical methods," explains Robert A. Hawsey, director of the superconducting technology program at Oak Ridge National Laboratory. It may be possible to introduce defects or create crystalline faults during processing. Researchers are also examining how to pin flux without introduc-

ing defects. The scheme, called intrinsic pinning, would try to sandwich vortices between the copper oxide layers.

Can the progress in applying the bulk materials be expected to continue? "There's a convincing array of data that makes us believe we are not facing sleeping lions," Malozemoff says. Among the earliest devices would be superconducting magnetic energy storage (SMES) systems. To store energy, the SMES coils are charged with circulating direct current. Because there is no resistance in the wire, the current could theoretically circulate forever. A utility could tap the energy when needed—say, during a power outage or during peak demand time. More important, it could dampen power oscillations, which can damage generating equipment. Bechtel in San Francisco is working with conventional superconductors to construct a 20-megawatt prototype the size of a football field. The high-temperature materials would vastly decrease the size of such a unit.

Several collaborative efforts that include organizations such as TCSUH, General Dynamics and American Superconductor plan to demonstrate components called fault-current limiters within the next two years. Such devices shunt power surges to prevent damage to lines and substations. Surge protection is at present accomplished by means of fuses and circuit breakers, notes Dean E. Peterson, the director of the Superconductivity Technology Center of Los Alamos National Laboratory, "and you have to send a repairman." Southern California Edison estimates it could defer upgrades and use cheaper fuses, saving up to $7.5 million a year on its power grid. Estimates for the entire U.S. are about $100 million a year.

Superconducting ceramics could improve the efficiency of power transmission itself, perhaps by the year 2000. A superconducting transmission line could carry three to five times more electricity than can a copper line. Existing underground lines use copper wire immersed in an oil that helps to cool the wire and saturates the insulation to provide the proper conducting environment. "Replacing the oil with liquid nitrogen is a no-brainer," Yurek says. Prototype transmission cable made by American Superconductor has carried 1,100 amperes over its length, about half of what EPRI thinks is necessary for commercial use. As Yurek sees it, "There's no technological barrier to getting this done."

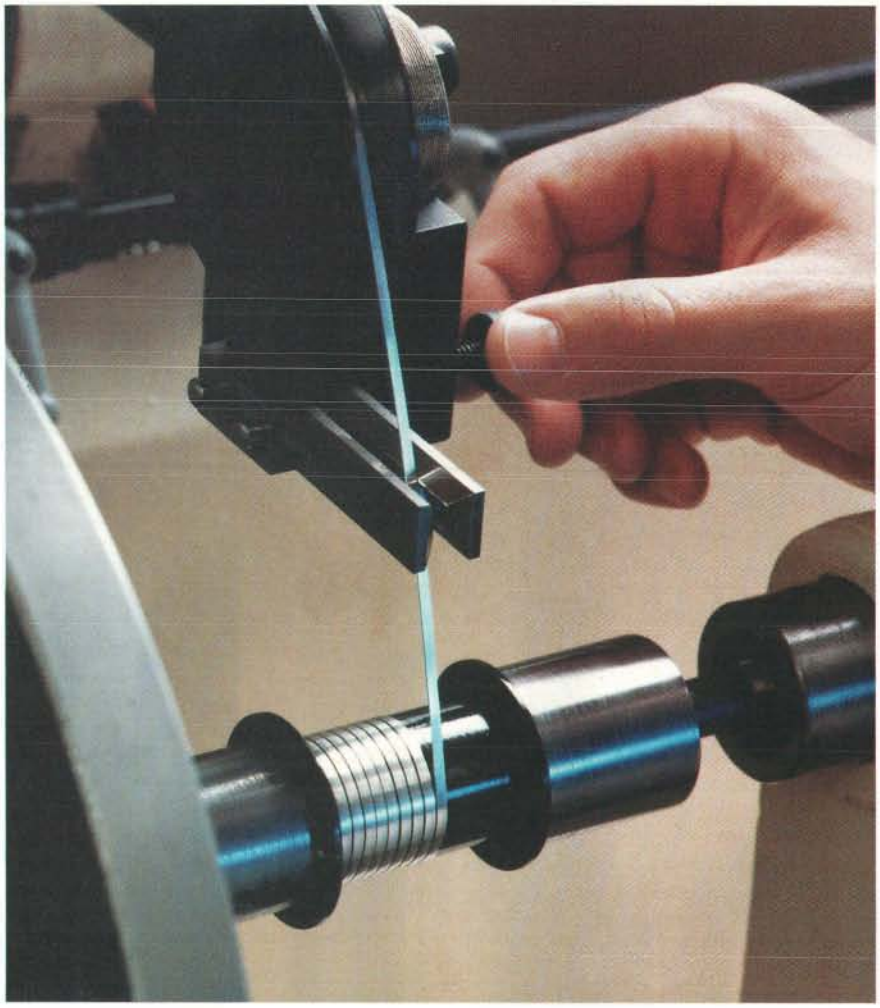
GREAT EXPECTATIONS: Paul C. W. Chu of the University of Houston floats a chunk of YBCO above an ordinary magnet. Chu recently reported that a mercury-based copper oxide under pressure superconducts above 150 kelvins.

Perhaps. But even if there are no "sleeping lions," the technology does face some additional obstacles. One is the challenge of cooling the ceramic materials. To keep the current density in the superconductor high, most applications will rely on mechanical refrigeration rather than liquid nitrogen. Using cryocoolers, which can chill down to 20 kelvins, is more expensive than cooling with liquid nitrogen (but is cheaper than doing so with liquid helium). The units can also be cumbersome. "What is needed is a relatively compact refrigerator that the customer is not aware of," says Conductus's Rowell. Another snag is the maturity of rival methods. Superconducting digital electronics, for example, may never leave the laboratory. "Silicon is a darn nice technology," CSE director Ralston observes.

Beware of Hockey Sticks

Some people in the industry glow with optimism about the economic future of the technology. In a recently released report, the members of the International Superconductivity Industry Summit (ISIS) composed of industrial

ANOTHER DAY, ANOTHER DOLLAR: a technician from American Superconductor removes a BSCCO cable from a dewar of liquid nitrogen for testing. In most envisioned applications, cryocoolers rather than liquid nitrogen will be used.



FLEXIBILITY of high-temperature superconducting wire is now sufficiently high that the wire can be wound into coils to make magnets.

groups from the U.S., Japan and Europe, estimated that the current $1.5-billion market for superconductors (for MRI and scientific research) will grow to between $8 billion and $12 billion by 2000 and to between $150 billion and $200 billion by 2020.

But other managers are not so sure. "The jury is still out on the issue of profitability," observes Carl H. Rosner, the president of Intermagnetics General. The ISIS numbers include sales estimates for ancillary equipment, such as computers that would be needed to process information from superconducting sensors. "You have to beware of hockey stick projections," Bell Labs's Bishop warns.

Even if the ISIS numbers are overly upbeat, at least several niche markets should emerge. The CSE has done its own analysis, and although it will not divulge numbers, William J. Gallagher, the head of IBM's effort in the CSE, intimates that several niche markets that add up to the size of current MRI systems will spring up this decade.

Greater inroads may hinge on discoveries of superconductors that have higher critical temperatures. That would mean a less costly coolant (such as freon or dry ice) could be used, or at least a larger margin of safety could be obtained with respect to keeping the material superconducting, Paul C. W. Chu, TCSUH's director, points out. "There really is no theoretical or experimental basis for a limited critical temperature," Chu says. The new mercury-barium-calcium-copper oxide compounds discovered this past March offer such a hope. One variety superconducts at a record-high 133 kelvins, and Chu reported in September that under pressure the critical temperature reaches 153 kelvins—within the range of freon. The early word on the mercury-based superconductors is that they pin flux better than do the bismuth or thallium families. But like YBCO, the materials suffer severely from weak links.

Even as the technologists wrestle with the physical properties of the materials, their colleagues in the front of-

fice are struggling to keep investment dollars flowing. To raise more money, Conductus and STI have both gone public this year, joining American Superconductor. Illinois Superconductor plans to do so before the end of 1993.

Although the 1993 U.S. budget for research in superconductivity is $246 million, it does not always aid businesses. "That's a lot of money, but it's mostly spent within the structure of the national labs or on decidedly defense-oriented research," says Kevin D. Ott, the executive director of the Council on Superconductivity for American Competitiveness, the industry's trade group.

Despite technological challenges and sticky finances, history may be on the side of high-temperature superconductors. "It's incredibly early," observes EPRI's Schneider. "The transistor was invented in 1948 and used commonly in radios about 12 to 15 years later." The laser experienced a comparable lag between invention and widespread application. "As I see it, the train is leaving the station," Yurek says. His optimism seems to be shared by American Superconductor's stockholders: the stock price of the company has more than doubled since its initial public offering in December 1991—despite posting numbers in the red (Yurek expects the company to break even by December 1995). "The message we are trying to get across is that superconductors are a reality," STI's Long says. "We need to press the engineering community, in effect, saying, 'Hey, here's another tool. Consider it, look at it and don't reject it out of hand as a laboratory curiosity.'"

Alan Schriesheim, the director of Argonne Lab, perhaps best sums up the feeling in the applied community. Like a field general, or a coach during halftime, he exhorts his troops: "The prize in the long run goes to those who stay the course in what is a long campaign. We cannot guarantee success, but we guarantee failure by getting out."

FURTHER READING

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Electronic Fireflies

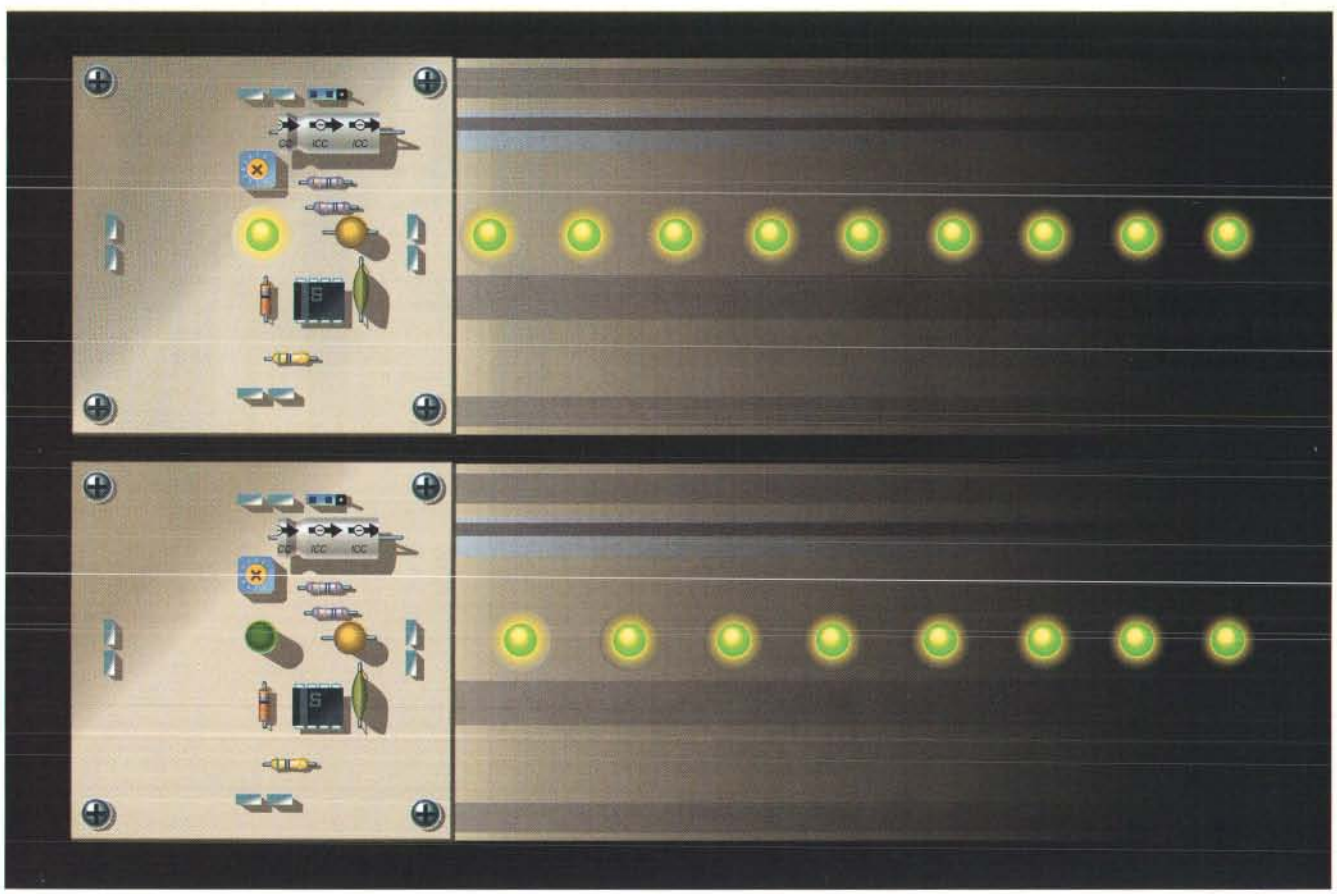
Biological oscillators generate patterns that range from the waves of peristalsis in the intestines to the walk, trot, canter and gallop of a horse. One of the most spectacular effects of coupled oscillation is the mass synchronization of thousands of fireflies of certain species. Steven H. Strogatz and Renato Mirollo proved how such synchrony arises by postulating a mathematical system based on an electrical circuit known as a relaxation oscillator [see "Coupled Oscillators and Biological Synchronization," by Steven H. Strogatz and Ian Stewart, page 68]. It is a fairly simple matter to build such an oscillator and watch the same phenomenon on a tabletop in a darkened room.

WAYNE GARVER and FRANK MOSS work in the department of physics at the University of Missouri at St. Louis. Garver is a senior scientist; when not building fireflies, he designs electronic equipment for the analysis of physical exertion during workouts. Moss is a professor of physics and biology. His current interest is the effect of random disturbances on sensory neurons.

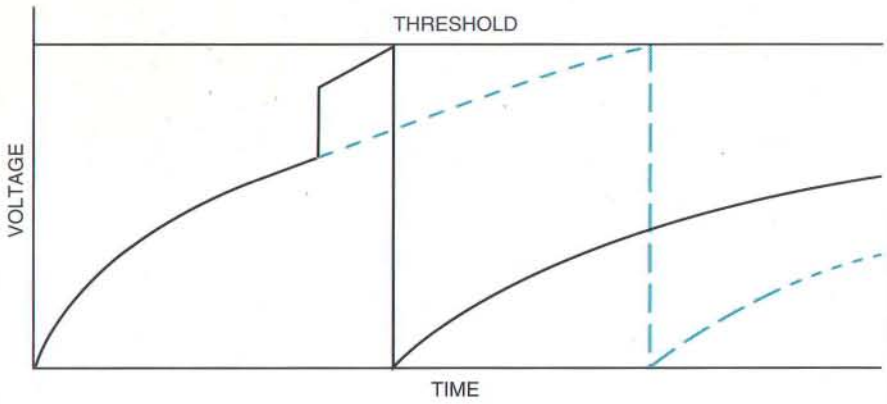
We wanted our oscillators to be as faithful as possible to our conception of how real fireflies synchronize as dusk deepens. Consequently, they are coupled by flashes of light. In daylight, their photodetectors are swamped by ambient light, and so each blinks at its own rate, but in a dark room they respond to each other's flashes and eventually flash in unison.

Our firefly works by pumping charge into a capacitor until the voltage across it reaches a threshold. The capacitor then discharges through a switch, the firefly flashes and the cycle repeats. If the firefly receives a flash from a neighbor, the amount of charge flowing into the capacitor briefly increases by an amount proportional to the strength of the flash. This increase makes the firefly complete its own cycle more quickly and thus brings the time of its firing closer to that of the one whose flash it received [*see top illustration on opposite page*]. After some number of cycles, the two will flash in synchrony. (This simple analysis ignores the firefly's effect on its neighbor's cycle, but as long as the charging curve slows as it nears the firing threshold, the two will in fact synchronize.)

What goes for two likely applies for a larger number, and so it would be natural to expect a large collection of firefly oscillators to synchronize as well. You will need to build at least two fire-



ARTIFICIAL FIREFLIES synchronize their flashes as each is affected by the other's blinking. They are controlled by a simple oscillator consisting of a timing circuit, a light-emitting diode and a phototransistor to sense incoming light. Multiple fireflies can be used for experiments that exploit rhythms that go beyond simple synchrony.

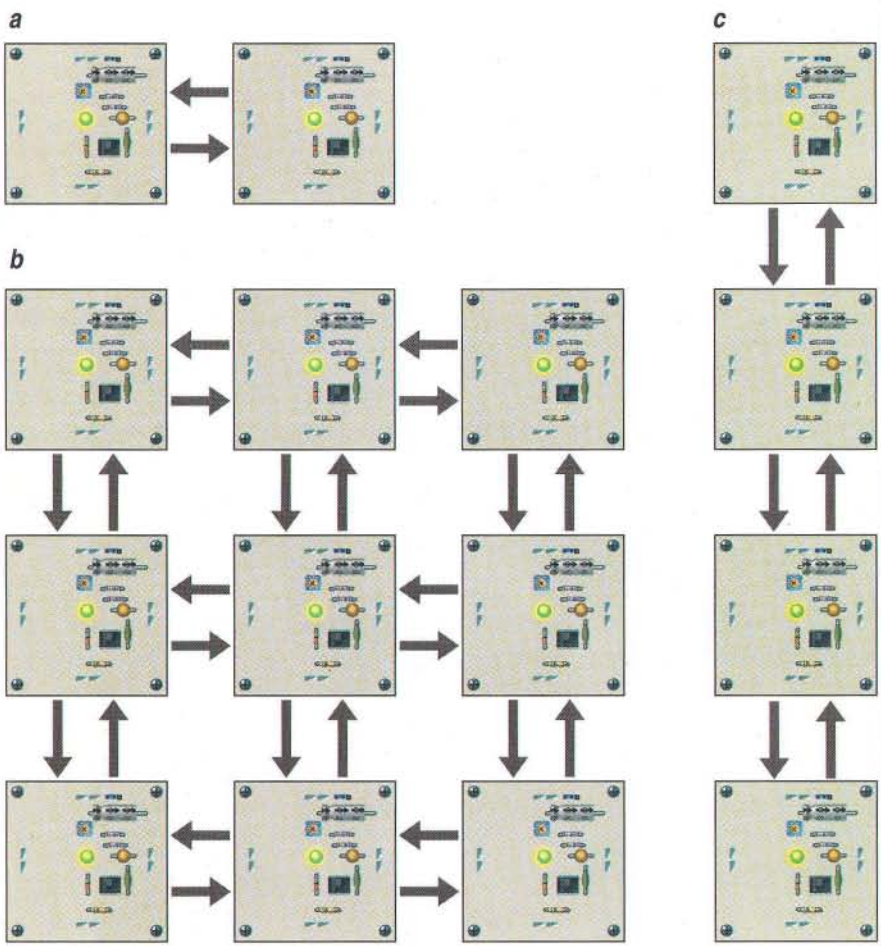


Advancing a flash

flies to observe synchronization, but three, four or even nine are better.

Probably the easiest experiment to conduct with the artificial fireflies is determining the time they take to synchronize as a function of the coupling between them. The stronger the signal that the phototransistors receive, the faster the devices reach lockstep. When you turn on the fireflies, they will be flashing at random. Place two fireflies a few centimeters apart with detectors and light-emitting diodes (LEDs) facing each other and turn off the light [*see* a *in illustration below*]; in a few seconds they will synchronize. The precise time required for synchrony depends on how far out of phase the fireflies are when the lights go off; for the most accurate results, you should make several trials.

To change the strength of the coupling between the fireflies, adjust the distance between them. The amount of light from an LED that reaches its neighbor's detector falls off as the square of the distance between them. Does the average time for synchronization follow a similar curve?



Some arrangements of artificial fireflies

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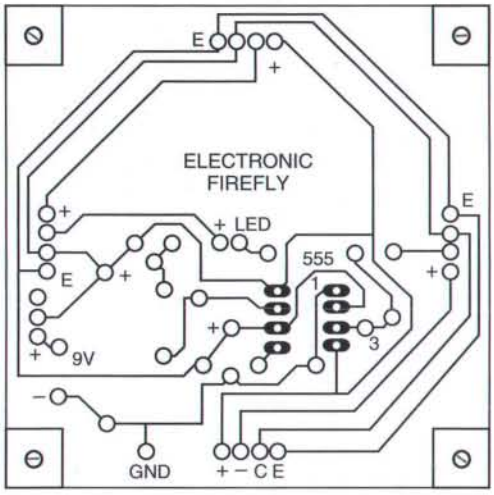
Building Electronic Fireflies

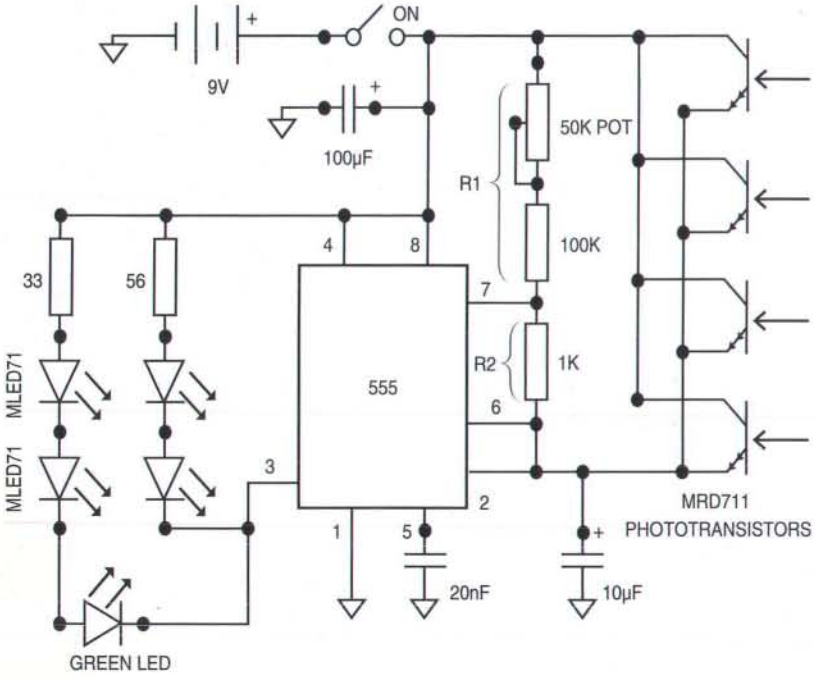
The heart of our device is an LM555 timer [*see schematic at bottom*]. The 555 is a workhorse for projects requiring periodic behavior. It has an internal switch that closes when the voltage across its control pins exceeds two thirds of its power-supply voltage and opens when the voltage falls below one third of the power-supply voltage. This dependence on voltage rations, rather than on absolute voltages, renders the device insensitive to minor variations, a crucial characteristic for a battery-operated circuit. The capacitor charges through resistor R1 and discharges through both R1 and R2.

Four infrared phototransistors (one for each direction) are connected in parallel with R1. When they "see" a flash of light, they conduct charge to the capacitor, quickly increasing the voltage across it and shortening the charging cycle. We have included a 50-kilohm variable resistor in the design so that the blinking of each firefly can be adjusted to roughly the same frequency. A rate of about one flash per second in the dark is best for most experiments.

When the capacitor discharges, the 555's digital output drives four infrared light-emitting diodes (LEDs), which send light to other electronic fireflies to bring them into synchronization. A green LED mimics the color of a natural firefly and tells the human experimenter that the firefly is flashing.

Although it is possible to wire a firefly together on a breadboard, concerns for reproducibility suggest a printed circuit. We used a kit available from Newark Electronics (4801 North Ravenswood, Chicago, IL 60640, (312) 784-5100) to transfer the circuit pattern (*reproduced at right*) to a copper surface for etching. One kit is sufficient for five fireflies. The cost of the parts for the nine we built, including the kits, was about $180.





With additional units, you can conduct more complex experiments. If you arrange nine fireflies in a grid, for example, the center one is coupled to four neighbors, the four edge ones are coupled to three neighbors each and the corner ones are coupled to two each [*see* b *in bottom illustration on preceding page*]. This difference can affect the rate at which they become synchronized. You can also change the grid spacing or interpose opaque barriers to change the number of units each firefly is coupled to.

Because of the way signals pass between our artificial fireflies, each one is effectively coupled only to its neighbors. As a result, a group of fireflies can oscillate in a rhythmic pattern other than simple synchrony. Arrange the units in a straight line about four centimeters apart, and turn out the lights to allow them to synchronize [*see* c *in bottom illustration on preceding page*]. Then use a piece of cardboard to break the coupling between the firefly at one end of the line and its neighbor; it will quickly go out of sync with the rest. When you remove the card, the resulting disturbance will propagate rapidly down the line. Changing the distance between fireflies reveals that this propagation speed depends very strongly on the strength of the coupling. (You can do the same experiment with eight oscillators arranged in a ring, in which case the disturbance propagates either clockwise or counterclockwise.)

All the experiments described thus far are based on the assumption that the oscillators' natural frequencies are similar enough that differences between them can be ignored—as in the synchronization proof of Strogatz and Mirollo. If you deliberately alter the frequency of one of the fireflies so that it differs significantly from those of the others, however, you can investigate yet another class of phenomena. One "oddball" firefly in the corner of an array of nine, for example, will delay the onset of synchronization for the rest of the array. Moreover, after a while the oddball will pull first a subgroup of its neighbors and then the entire array out of synchrony. In this case, the coupling between oscillators ultimately works to destroy order rather than to create it.

FURTHER READING

SYNCHRONOUS FIREFLIES. J. Buck and E. Buck in *Scientific American*, Vol. 234, No. 5, pages 74–85; May 1976.

TALKING TO STRANGERS. David Attenborough's *Trials of Life*. BBC Television, 1991. Distributed by Time-Life Videos.

WHERE MIND MEETS MATTER IN GERMANY.

SPEKTRUM DER WISSENSCHAFT, established in 1978, made in Heidelberg, is the German-language edition of Scientific American. It delivers a substantial and highly educated readership among the scientific community, decision-makers in government and industry, and technical and research management. Paid circulation: 120,000. A member of Scientific European Network.

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Science Books for Young People

The Earth

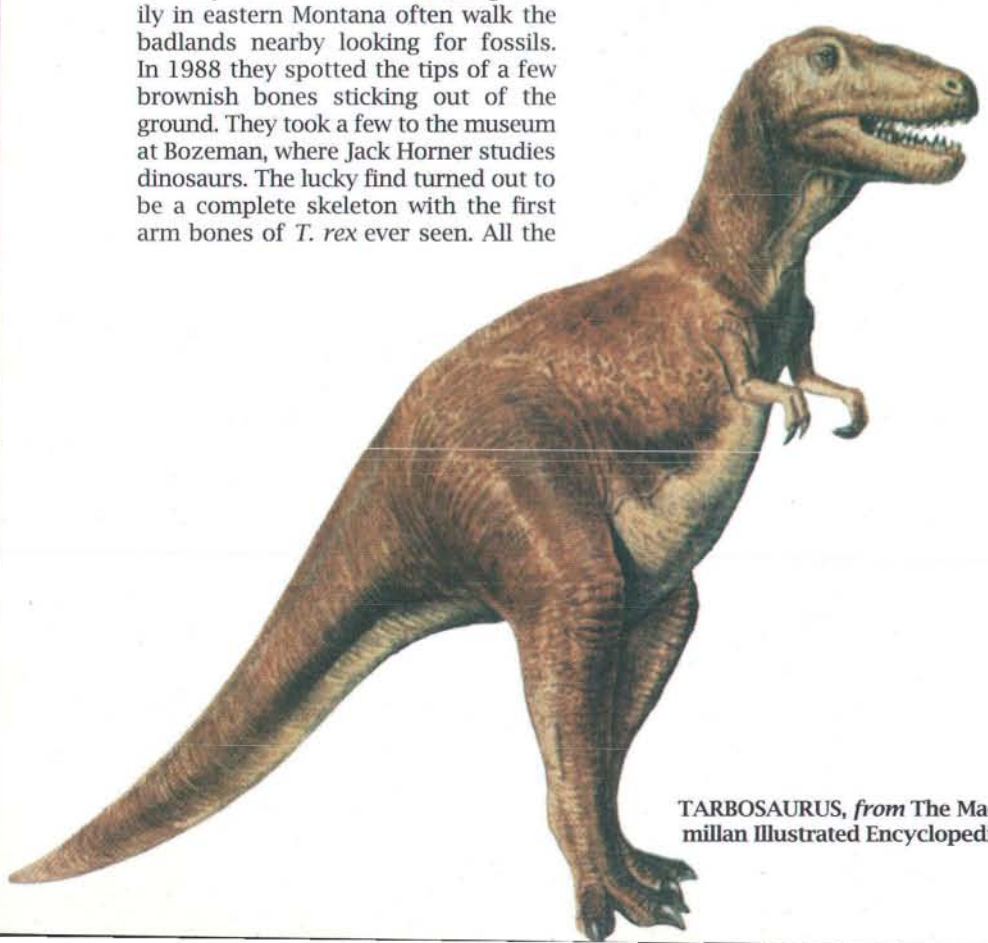
DIGGING UP *TYRANNOSAURUS REX*, by John R. Horner and Don Lessem. Crown Publishers, 1992 ($14).
THE MACMILLAN ILLUSTRATED ENCYCLOPEDIA OF DINOSAURS AND PREHISTORIC ANIMALS: A VISUAL WHO'S WHO OF PREHISTORIC LIFE, by Dougal Dixon, Barry Cox, R.J.G. Savage and Brian Gardiner. Collier Books, Macmillan Publishers, 1992 (paperbound, $25).
THE DRAGON IN THE CLIFF: A NOVEL BASED ON THE LIFE OF MARY ANNING, by Sheila Cole. Drawings by T. C. Farrow. Lothrop, Lee, and Shepard Books, 1991 ($13.95).

Tyrannosaurus rex is a superstar, all right. But this small book for dinokids is about one real ancient lizard, not about fictional animation. It tells the story of who found it and where and how the bones were taken home and put together and what they tell, a tale not yet finished.

Kathy Wankel and her ranching family in eastern Montana often walk the badlands nearby looking for fossils. In 1988 they spotted the tips of a few brownish bones sticking out of the ground. They took a few to the museum at Bozeman, where Jack Horner studies dinosaurs. The lucky find turned out to be a complete skeleton with the first arm bones of *T. rex* ever seen. All the *rex* images we had seen, ever since the first bones were taken out of Wyoming rocks in 1900, were based on analogies.

The Bozeman team came, dug out and plaster-packaged the 40-foot skeleton. With the help of the army engineers and their backhoes and flatbeds, they hauled it all back to the museum, where it has been cleaned of rock and fitted together over the years, tiny bones and big. It was a grown-up saurian, for its bone cells look mature under the microscope. The arm bones are about human size, but marks of muscle attachment show that the arm muscles were 10-fold stronger than ours. Could they have held down a struggling duckbill?

We do not know enough yet to be sure of the real *T. rex*, whatever you see on the screens or even in the museum mounts. We have no eggs, no babies, not even footprints, to show how fast it walked or ran. But we are finding more of these extraordinary fossils, nearly complete. Even in the few years since Kathy's, two more are being worked on, out of only 10 found this century. The sites are marked on a map, and you will also see how four or five museums once decided to mount their fearsome specimens. If you come West and find another one, call up Jack Horner right away. Together you can dig it up, and someday we'll all know what the tyrant lizard king really could do outside the animator's studio.



TARBOSAURUS, *from* The Macmillan Illustrated Encyclopedia

Science is based on the evidence and tested by the evidence. But it must grow beyond the evidence, or fossils remain mute jumbles of dry bones. Evidence is built into an emerging structure of ideas. The encyclopedic illustrated paperback from Macmillan, "a visual who's who" of ancient life, is a rich collection of some 600 hard-edged color paintings, each one a named fish, amphibian, reptile, bird or mammal from the past, drawn against a white background. The work of a dozen British artists and consultant biologists, it derives from and illustrates such a structure of ideas, as they were held in the late 1980s. It is as it must be, at once authoritative and approximate. Check out *T. rex:* pretty good!

Maps of the shifting world, charts and family trees, geologic timescales and a flood of brief descriptions group by group approximate a view of all life since the vertebrates began. Those who seek to flesh out paleontology will find this a fine reference; it includes many thousands of generic names. Reading families, school classes and libraries will all benefit, although the terse prose and many graphs and charts are on the whole rather formal.

The third book here is quite different. It is a brief novel, an artist's effort to imagine from fragments of evidence—the letters, daybook and records of happenings—the richness of a human life in a small English coastal town at the time of the Napoleonic Wars.

We read of the thoughts and deeds Cole has imagined for the real girl, Mary Anning, as Mary grew from seven to 16. Mary lived with her family near the sea cliffs of Lyme Regis. Born 10 years before Charles Darwin, she understood what her father had taught her: collecting fossil signs of past life from the limy cliff was both fascinating to a curious mind and worth real effort. The early death of her father, a cabinetmaker whose own unprecedented interest in fossils had brought well-off collectors

to his door, challenged Mary to maintain her thoughtful, risky patrol of the cliffs and their debris against the narrowness of her neighbors and friends, who saw no good in a poor girl's intellectual curiosity. She struggled internally against doubt, scorn and mistrust, externally against the dangerous waves and the long tedium of search, and the even higher barriers of gender and class. Her wealthier customers often drove unfairly hard bargains and then claimed credit for what she had found, spiral ammonites and big single vertebrae to begin, at last the wonderful large bones of the first icthyosaur ever seen. For a while, her searches were joined by young Henry, a wealthy amateur of the town, and the dreams of a romance are warm and winning. But Henry moves away. And the novel ends with an evocation of the intellectual and moral struggles of a gifted young woman: "It is somewhere between...the Lyme of my neighbors and the...geological gentry that I must find a place for myself."

There is a factual epilogue. An obituary for Mary Anning, who never went beyond a few years of school, was written by Henry de la Beche, gentleman founder and first director of the Geological Survey of Britain, on Mary's death of cancer at 47, "with fortitude." She was one, he wrote as a lifelong friend, "who had to earn her daily bread by her labor, yet contributed by her talents and untiring researches in no small degree to our knowledge of the...organic life entombed in...Lyme Regis."

SURTSEY: THE NEWEST PLACE ON EARTH, by Kathryn Lasky. Photographs by Christopher G. Knight. Hyperion Books for Children, 1992 ($15.95).

It was at dawn on a November day in 1963 that Icelandic fishermen a few miles offshore smelled a strong sulfurous odor, saw something smoking in the sea to the north and radioed the coast guard to inquire whether some ship was burning. By 10 in the morning they knew from the feathery columns of ash two miles high that the fire was a volcano under the sea. The island appeared above the waters about 24 hours after that first alarm.

Iceland itself is such an island, much older and larger, on the volcanic Mid-Atlantic Ridge, so Icelanders have known about such matters for a very long time. Their famous poet wrote of fire and sparks from the sea, of earth rising up and sinking again. Each chapter here opens with lines Snorri Sturluson wrote eight centuries ago.

The dramatic book for grade school readers by this team of adventurers tells the story in two exciting acts. The first was the birth of Surtsey, named after Surtur, the god of fire, who once came, the poet says, to fight the poison-spitting serpent from undersea. It was Icelandic sailors and scientists who originally studied the place; their account and many pictures are here, at first all surf, flame, lava and sintered ash from two cratered cones high above three square miles of new land.

The first plant took root on the little new world within 18 months, its seeds brought by some bird. Spores blew in, and more seeds arrived by sea and air. Our travelers came to rocky Surtsey in 1991 to report what has happened there now that life has found its way. The sea is rich with fish, and no predators hunt the land, so that many seabirds have chosen to nest safely on the freshly formed cliffs. You can see white flowers bloom, green mosses and algae grow, and birds circle in flocks on the newest place on the earth, past wisps of blue vapor that still curl upward from that fire deep underground.

CHILDREN OF CLAY: A FAMILY OF PUEBLO POTTERS, by Rina Swentzell. Photographs by Bill Steen. Lerner Publications Company, 1992 ($14.95; paperbound, $6.95).

People in Santa Clara are happy to live in that beautiful setting below the Jemez Mountains, where you look across the flowing Rio Grande nearby to the far high ridge of Sangre de Christos. A hot summer day is a good time to fetch the brown-orange potter's clay with a mica sparkle from the cool of the mountains. Gia Rose has done this for a lifetime; it is she who tells the myths as they all go off together by pickup and car, eight persons of four generations, Gia Rose to the youngest of her 17 great-grandchildren. They dig from the clay pit once Gia Rose has explained their intentions to the spirit of clay, Clay-Old-Woman. She thanks her and promises respect in the use of the wonderful material. Men help dig, but in Santa Clara pottery is women's work.

The clay is soaked for days, screened for twigs and stones, laboriously mixed with fine white sand, until sitting together they form it, coiling, pinching, pressing and smoothing it into pots and bowls and animal figures, both new forms and those of old tradition. Once these were made only for Pueblo use; nowadays they are sold to visitors and to art dealers faraway. Children, too, make and sell their figures. The careful steps of fine handiwork production, often including painted decoration, are done outdoors by shifting family groups. Most dramatic is the final wood-fueled firing, where you can hear the cracking of those few pieces Clay-Old-Woman did not help endure.

This fine account for young readers conveys a sense of home in the context of fully shared work. Thus, the book is as much an insider's look at thriving village life as it is a glimpse of a living craft 100 centuries old. A brief folktale, some designs, a few Tewa words and a good map of Pueblo country support the evocative photographs. Dr. Swentzell is herself a potter from a Santa Clara family of potters; Bill Steen is a notable photographer of the Southwest, who has strong ties to Santa Clara.

Math

ONE MILLION, by Hendrik Hertzberg. Times Books, 1993 (paperbound, $14).

Two hundred genuinely dotty pages make up this book. On each carefully numbered page stand 5,000 big, black printed dots neatly arrayed by column and row into a large triangle: altogether one million. You will search a long time to find a wiser introduction to the natural numbers and what they mean.

Of course, the usual counting book, 10 or a dozen sets of elves or bananas, is right for the very youngest. This nifty volume is for those clever kids, no longer beginners, who can count right now as high as anyone is willing to listen to. (A million out loud is a week's work.) They may well claim to know what a

million is, all right, but "to 'know' something... and to experience it concretely are two very different things."

This single example of a concrete million would poster both sides of a school corridor or paper over a whole bedroom wall. Real counted-out millions are hard to come by, and if you want to view a billion dots—

The talented author, now a senior editor, knows that the very generality of repeated units, just what gives them their awesome power, makes abstract enumeration dull. He made his lengthy, austere set into a lot of fun by promoting a few dots—about one in 1,000—to symbolize something far from paper and ink. Each such dot is left out of the parade, reentered above, while a line points out its place in the serried ranks. The few words that define what it counts, provocative or whimsical, are printed beside it in red. On the first page, note, after counting the small population of Eden, that 1,860 steps take you to the top floor of the Empire State Building. Go much farther to count the nearly half-million-ton weight of a record swarm of locusts; by the next-to-the-last page, on some reckoning, the number of interracial married couples in the U.S. is 994,000.

This wonderfully original, now updated book first appeared 20 years ago; author and dollar were younger, and the book cost 395 cents.

DEAD RECKONING: CALCULATING WITHOUT INSTRUMENTS, by Ronald W. Doerfler. Gulf Publishing Company, Houston, 1993 (paperbound, $17.95).

The fabled lightning mental calculator is no more or less a wonder worker than is the slam-dunk basketball pro, able to perform the same sequence of moves we would all need with exceptional reliability, precision and speed. This author, an engineer with a keen sense of number and a flair for numerical analysis, has found and put down a reasoned set of stratagems for fast mental calculations (not excluding paper and pencil) that allow impressive numerical approximation to the elementary functions without prodigies of memory or the gift of lightning.

The first 70 pages outline dead reckoning using the four functions (division, not easy to simplify, is "a construct of man," although the others share the Divine). It is of little use to outline all these clever procedures: enough to point out the importance of operating on groups of digits and of manipulating numbers into more pliable forms. That is "where the fun lies."

Take the identity $(a+b)(a+c) = a(a+b+c)+bc$. Once even second graders learned to find 8×7 from $10-2$ and $10-3$, thus $10\times5+2\times3$. "Why not?" Recurring decimals offer fine long strings for answers. Try $^1/_{43}$: long division easily gives 0.023 plus $^{11}/_{43}$. Now $^{11}/_{43}$ is easy, then $^{121}/_{43}$ takes you out to nine digits. In three more lines of similar artful attention to remainders, the text shows 21 digits. That is all there are; the rest recur.

Even more remarkable is a method for square roots based on extension of the Newton scheme for finding roots by iteration. One quickly outdoes the hand calculator: a 16-digit square root of 51 is about as far as you can verify without fancy software beyond double precision. As a challenge, these procedures will attract many adepts. But they are equally attractive for study and discussion among good students who want to be at home with elementary functions though loyal to the keypad. "I am quite sure," writes the author with sufficient reason, "that you will not find another book like this one."

Perception

HIDDEN PICTURES, by Linda Bolton. With mylar mirror. Dial Books, 1993 ($14.99).

A grotesque giant head lies half buried in the sand. Or is it a group of people sitting in front of their round hut? Giant's bushy hair or tangled bushes? The painter Salvador Dali made it both at once. Here are a couple more of Dali's visual puns, a few of the cunningly interlocked figure grounds of M. C. Escher, a wonderful landscape-giant by a 17th-century Spanish painter—the giant's nose is a slant-roofed tower—and a Giuseppe Arcimboldo portrait of a man's head that is only a stack of animals—camel, lion, monkey, sheep. Besides all these, there are a dozen jumbled puzzle paintings, to be read by looking at their reflections in a cylindrical mirror. Across a spread are two handsome lines of Leonardo da Vinci's mirror writing. Add the René Magritte window glass with a painted sunset, broken so that we can see through the gaps to the matching sunset outside—or in fact to one more painting?

This small delight of a book not only provides the cylinder mirror you need but also shows how to make a double picture, dragon and boar at once by a small shift in viewpoint and a puzzle drawing of your own, made just as they were painted long ago.

TURNTABLE ILLUSIONS: KINETIC OPTICAL ILLUSIONS FOR YOUR RECORD TURNTABLE, OR 101 USES FOR AN OBSOLETE TURNTABLE, by John Kremer. Open Horizons Publishing Company, 1992 (P.O. Box 205, Fairfield, IA 52556) (paperbound, $9.99).

Every page here has a central hole for the spindle. First find a turntable at 33 or 45 rpm. (If you haven't one, it isn't too hard to spin the pages on a pencil.) The author has assembled a wild set of black-and-white spirals and rays and checks and rings, even off-center white ellipses on an all-black disk. Spin them before your eyes with good lighting, and you will see much more than text can describe—colors, moving afterimages, figures that seem to expand and contract at once, springs and volcano cones cavorting and erupting forever in three-dimensional space, awry wobbles and wriggling amoebas, and a good deal more.

Most of these effects have discoverers with names, perception research people back to Johannes Purkinje in the 1820s; some we owe to gifted artists, especially Marcel Duchamp and Hajime Ouchi. Others were found by John Kremer himself. The book gives a plausible brief account of every one of these effects; a few are quite well understood in terms of the visual system. "See for yourself."

An alert is worth sounding: these patterns may induce epileptic seizures in susceptible persons. Otherwise they are open to all ages.

ANIMALS OBSERVED: A LOOK AT ANIMALS IN ART, by Dorcas MacClintock. Charles Scribner's Sons, 1993 ($18.95).

Three views of a zebra amount almost to an inspired engineering drawing of the stripy wonder, even though they were done centuries apart. Rembrandt's elephant in crayon "looks about for more hay" and shares the page happily with a superb silhouette cut by Ugo Mochi of an African elephant stripping a tree it has just felled for its bark. The gray tiger cat who looks so eagerly, mouth open, ears forward, at a frightened caged finch, "perhaps the best cat in art," is only a background detail in a 1742 portrait by William Hogarth of four rather distracted and dressed-up children. The book is a prize for any willing reader who loves animals and has someone to answer a few questions about words.

Life-forms

TENTACLES: THE AMAZING WORLD OF OCTOPUS, SQUID, AND THEIR RELATIVES, by James Martin. Crown Publishers, 1993 ($14).

What a title! What a topic! It is, of course, those tentacles that draw the mind, whether, like those of a grown-up giant squid, they are the size of a run of fire hose or finger-sized like the 90 intricate ones that surround the mouth of the chambered nautilus to provide it with both touch and taste.

Some deep-sea squid are studded with luminous organs that glow colorfully; others harbor entire lanterns of glowing bacteria. Six-foot-long Humboldt squid hunt the sea like jet-propelled wolf packs, if less cunningly. Octopuses are here, too, from a sleepy, big red Pacific one that lets divers pet it to a blue-ringed Australian, no larger than your fist, with a deadly poisonous yet strangely painless bite. The baby octopuses, transparent fingernail miniatures of their parents, may hatch by tens of thousands, but only a dozen are likely to mature.

All these cephalopods (their name means the head-footed ones) are mollusks, kin to the clam; most have no shell and no bones save a small remnant within. They are intricate bags of tough muscle, with plenty of control, swift-changing skin colors, good-sized eyes and tough beaks, alert, often even intelligent. No group of animals has so much in common with us and yet so utterly different a body plan.

In 30 easy pages, amid many images, James Martin has brought young readers exciting glimpses into a bizarre and intricate world of life we are only now beginning to appreciate. Any beach on the open ocean might hold the remains of a giant squid; don't forget it! Meanwhile visit the aquarium but look beyond those comfortable cousinly fishes to folk with tentacles.

JACKAL WOMAN: EXPLORING THE WORLD OF JACKALS, by Laurence Pringle. Photographs by Patricia D. Moehlman. Charles Scribner's Sons, 1993 ($14.95).

It is the wet season right now on the Serengeti plains. Most likely Patricia Moehlman is there, quietly watching golden jackal families in the grasslands and the silver-back jackals in the wooded bush nearby. She watches from her old Land Rover without disturbing them—"It is hard to just sit and watch when pups are sick"—for they tolerate her discreetly shielded presence 100 feet away. She knows these animals well by the names she gives them after some natural mark, for she has long followed them, some pairs for close to a jackal's lifetime, seven years. These are beautiful creatures, beautifully imaged in this small book. Their joyful leaps and their endearingly fuzzy, bumbly, eager pups in no way fit the old metaphor of timid petty thieves. Jackals exploit kills of the big predators when they can, but most of their food—fruit, rats and mice—they earn the hard way.

Jackal parents share remarkably equal roles. The couple hunt and defend territory cooperatively; once the male has for weeks brought food to the nursing mother in the den, they join to feed and rear the litter. Young adults are ready to leave the family at 10 or 11 months. Some do, but many remain to help rear the next litter of pups. Those forgo for a while their full maturity, although they guard, groom and play with the pups and hunt for them all as if they were the parents. With such helpers, more pups survive. It is striking that the goldens, usually gentler, tolerant, more playful, turn sharply less caring whenever food is scarce. Yet the silver-backs, who live where food is more abundant, appear much less affectionate and have many fewer helpers. Jackal society, too, depends subtly on economics.

BACKYARD SUNFLOWER, by Elizabeth King. Dutton Children's Books, 1993 ($13.99).

Deft and sunny, this little book opens with the image of a golden sunflower bigger than Samantha Nolet's head and well above it, too. It had started out as one striped seed among the few she had planted that spring, carefully spaced, in her backyard flower patch somewhere near Fargo, N.D. The patch needed water without fail; you had to be careful as well as patient. In a week, the plant was a tiny sprout. In a month it was two feet high; Samantha measures it before us to show off the big, soft green leaves and thickening stalk. Each day the leaves would turn to face the sun as it rose and set. Soon the plants were tall and thick enough to shade her.

When the bright golden flowers were full grown, they stood so high the children had to find a ladder to reach the flower heads where the seeds were ripening in their wonderfully regular pattern. Soon the big heads dried and drooped for easy harvest. Birds love to eat the tasty seeds. People do, too, especially after roasting them, but like Samantha they always remember to

save some—to plant the following year.

The photographs here are utterly winning; young readers need grasp only six or eight interesting lines of text per page. Everyone knows that even around Fargo life is not always sunny; dark days will come. But these sunflower kids, seven smiling friends perched on ladders, make sunny days vivid.

Experiments from Books

A much-needed genre of science books for young readers seeks to open the world of experiment. Such books face a hard task: using words and images, symbols of necessity touched by the abstract, they aim to evoke action in a concrete world. But that is the essence of science, and all effort toward that end deserves attention and support. The pitfalls are many. Perhaps the simplest of them is mismatch between the objects the author intends to use and those that are in fact at hand. Neither households nor marketplaces are universal; the beginner cannot easily substitute. The book trade has not often distributed boxes of varied gear, although packaging with a book small, key tools—magnifiers, maps, eggs and seeds—is a hopeful current trend.

The hallmark of most experimentation is replication, usually followed by modification. At once, barriers of effort and tedium arise. If a book is to bring readers to study its text closely, it must motivate readers strongly. So much the more if it is to lead to record-keeping and deliberate replication. An experimenter needs to find pleasure in such actions themselves; consider the kids who throw tirelessly at the hoop.

It is easy to see how a wide-ranging experiment book, one that treats many branches of simple physics, chemistry or biology, is in danger of being too demanding. A book on a narrow topic risks a much narrower readership but has more chance to engage its readers. Generalities can be drawn from experiments that of necessity deal in minute particulars but seldom begin there.

New experience is the aim of experiment, but experience is also a prerequisite for consistent experimentation. Just messing about with water or light or balances or salt solutions or growing molds is indispensable. The jargon word is readiness. That takes time, defers satisfying closure. Certainly the style fits younger more easily than older readers, for growing up itself is managed by much the same means. Games, puzzles, models, art and literature can very well accompany books that aim at increasing readiness. Such texts may need to stay at a remove from detailed laboratory setups. The engaged growing of animals or plants across their life cycle (call it husbandry or gardening) is a splendid domain for gaining deep experience in the life sciences.

Experiment follows, often even depends, on just that kind of entry. After that richness, usually inexplicit and varied, controlled and disciplined lab experience can go far. It demands something approaching the time, the preparation and the resources of a high school course, not readily trapped in a book. But a broadly aimed book opens a wide gate, sometimes even when it seems narrow. Books that help a kid carefully build a radio or grow a plant without much concern for conceptual growth are of value elsewhere.

A final pitfall is the small tyranny of shibboleths and pat formulas that remain hollow. Light travels in straight lines; many books we see are firm about it and even "prove" it now and again. Are rays straight if they are broken by reflection? What about heat shimmer? What about the spherical wave fronts that spread from a source? The growth of successive approximation, the necessity of alternative accounts, is essential to real experiment. Otherwise you might well call it rigged.

For such reasons, we have never included many of the books we see that propose laboratory experiments for young readers. A large number of them are good of their kind, but they require cautious matching to circumstances and usually imply some sympathetic adult help at hand. It seems to us that the best books here demand two kinds of understanding from their authors: a true grasp of experiment, probably gained from much lab experience, and detailed understanding of how the particulars are handled by young people, probably based on actual trial. Now for two contrasting examples of experiment books that we recommend highly.

REAL LIVE SCIENCE: TOP SCIENTISTS PRESENT AMAZING ACTIVITIES ANY KID CAN DO, by Jay Ingram. Illustrated by Tina Holdcroft. Firefly Books, Buffalo, 1992 (paperbound, $8.95).

The author, who is a Canadian radio science show host, has made for middle school readers and older a book that soars. It offers a cheerful page or two by and about 21 "real live scientists" at work in Canada. These men and women each sketch some experimental action in a page or so, sometimes the work of an hour, sometimes demanding months. All experiments are left open to variants, all tied, if very loosely, to larger meaning.

Try to see the remarkable illusion called Bidwell's Ghost, which resembles but is not an afterimage; you need a flash camera and a truly darkened room by night. Record as best you can the hour-by-hour activities of someone in your family for 10 days, and compare your results with the orangutan records shown us here by famous anthropologist Biruté Galdikas from Borneo: you share her very research, save that your primate subjects are even more interesting if much less rare. Make digital portraits of yourself and your friends, then check their recognizability, or read underwater, again with tests, or debate the surprising statistics you collect from a chancy game of hiding and guessing. Work with "hot ice" and lava pancakes; test your own bug repellents. This brief book makes as good a join between the broad conceptual field and the experimenter's focused view as any a reviewer can recall. Of course, it demands genuine initiative; its admirable guidance is short on detail, long on motivation.

MOBILES: BUILDING AND EXPERIMENTING WITH BALANCING TOYS, by Bernie Zubrowsky. Illustrated by Roy Doty. Beech Tree Books, William Morrow & Company, 1993 (paperbound, $6.95).

This is a book in contrast with the one above: no scientists, aimed strictly at 10 years old and up, a narrow if deep-lying piece of physics, sketches of kids and acrobats, drawings with step-by-step details, all thoroughly tried out in schools and at the Boston Children's Museum. Its interest is pure: neat things happen as you try push-ups, build cardboard body models and move beyond easier symmetry to more challenging oddness, even toy wire walkers. The small book bears one hallmark of science often neglected: experiments evolve. Seesaws can balance on seesaws, on to tricky mobiles, even Alexander Calder. End with the law of moments made practical. But here, too, is "real live science."

This is likely to prove more work than one kid can do; partners and groups are natural. Companion books in the same vein treat model timepieces, balloons, tops, straws and more.

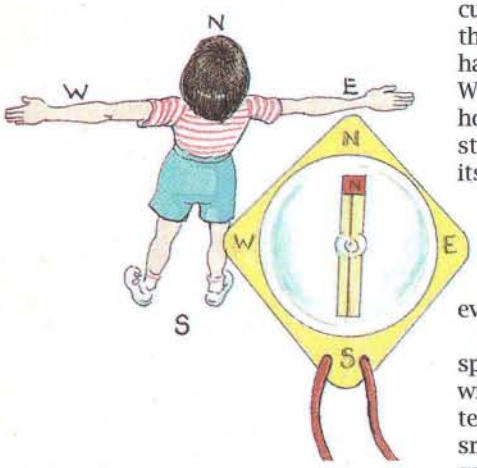
Out-of-Doors

THE PATHFINDER'S ADVENTURE KIT, by Christine Kennedy, Mark Smith and Pat Hancock. Illustrations by William Kimber. A Somerville House Book, Random House, 1993 ($15, in transparent carri-

er with paperbound handbook, study map, route markers and compass).

NAVIGATION: A 3-DIMENSIONAL EXPLORATION, by Anne Blanchard. Illustrated by Irvine Peacock. Orchard Books, 1992 ($15.95).

These two interesting offerings bring ideas of navigation and mapping to grade school readers by using more than pictures and text. The *Adventure Kit* has a well-written little book that centers attention on a colorful map of an imaginary town, Jefferson. The map is supplied as a poster that unfolds to about 18 inches square. The notions of the plan view, scale, symbols, and even grids are brought out by setting simple tasks of route and location. The ideas are extended to maps galore, to world scale and the subway. Map your room, then your route to school. All these aids to learning are done lightly enough to please and not to burden.



A pathfinding game closes the book and brings it to the beginner's edge of real orienteering. This kit can fulfill its promise if, and only if, the reader—or better, a small group—will spend the time it takes to do something and not just read over the brief text. The transparent compass supplied is simple and well made, but some warning about the wayward magnetism of urban homes and streets would have been useful.

The book on navigation is another artful introduction for grade school readers, embellished by pop-ups and similar mobile paper elements. First of these is a pop-up model of Columbus's *Santa Maria* under way, all sails set. There are strips you can move to show winds and currents on the oceans, models of radio and lighthouse beams, a pop-up GPS satellite and more. A sextant model has an agreeable moving arm along its graduated circle, although the pop-up papery mirrors are not flat enough to demonstrate clearly its simple but clever optics. Text, color and the promise of working out the pop-ups add enough interest to make the book attractive to good readers with a little tolerance for simple mechanical trouble and the wit to mend it.

INSECTS IN FLIGHT, by John Brackenbury. Blandford, London, 1992 (distributed in the U.S. by Sterling Publishing Company, New York), ($35).

Insects are small, fast and unpredictable. To fill these big pages with stunning portraits of hoppers and jumpers and beetles and butterflies in midair took a lot of doing. This University of Cambridge biologist knows how to draw a reader in deep without jargon or mathematics; he then explains clearly the surprises he has documented about insect leaps and flights.

These 100 color images are an edited 1 percent of his shots over four years of work. "Often I would find a well-focused 'foot' suspended mysteriously in the...corner of the picture, its...body having completely eluded the camera." What he is after just now is the froghopper, who by daylight leaps high in streamlined trim, to slow down once its wings open—maybe. Brackenbury's new home-built shutter opens in three milliseconds; once it is open, the flashgun pops electronically. But the agile froghoppers still evade his camera.

Insect flight—the structures, strength, speeds, control and the rest—is tackled with visual support over nine full chapters. The text examines as well what small fliers (and jumpers) pay for and gain from this engineering, a third airborne way unlike bird or plane. Yet the feathery wings of fairy flies seem to be more birdlike than was once thought, not a way to move by viscous drag, as if through syrup.

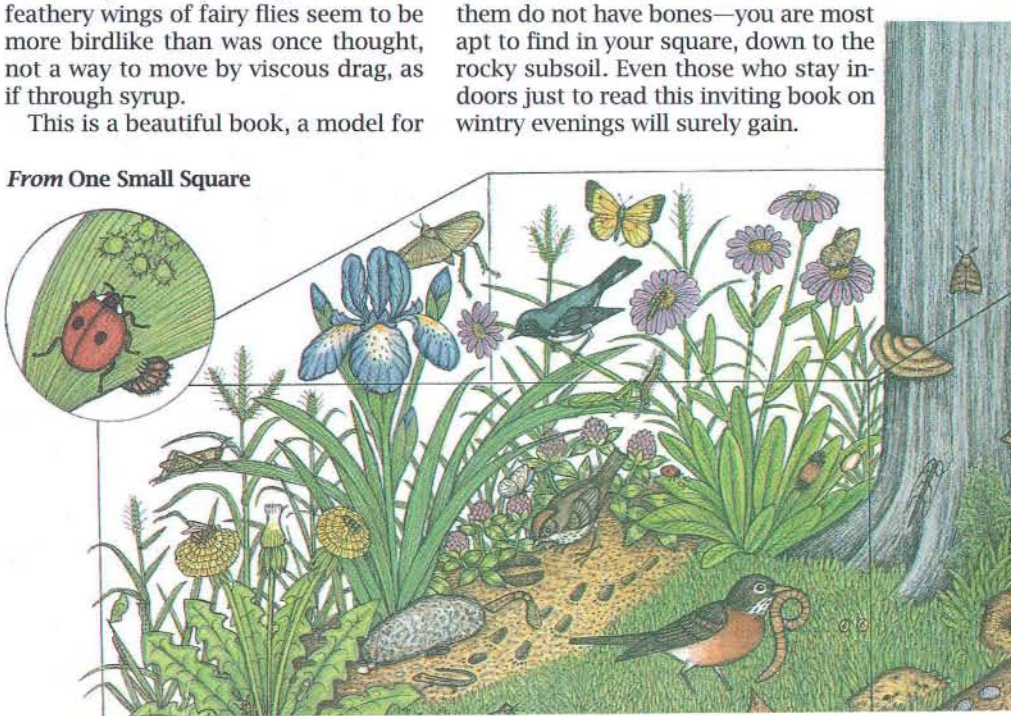
This is a beautiful book, a model for serious readers who like to study life, image it or grasp its subtle physics and are prepared to pay close attention to really good stuff.

OUTDOOR SCIENCE PROJECTS FOR YOUNG PEOPLE, by George Barr. Illustrations by Jeanne Bendick. Dover Publications, 1991 (paperbound, $3.95).
ONE SMALL SQUARE: BACKYARD, by Donald M. Silver. Illustrations in color by Patricia J. Wynne. W. H. Freeman and Company, 1993 ($14.95).

The first of these admirable books is a very modest guide to strolling research. Any electric poles nearby? What are they made of? Look for insulators, then for transformers; are you on the way to the substation? (Listen, too.) Bustling city street or quiet meadow, both are full of interest. Stones, trees, plants, insects, birds and sky are the topics for very diverse hints, questions and brief keys to new experience. The birds here are not exotics but 20 species common in the city; the sky is examined by day and by night, and there is even a proposal, among many more, to make fog in a bottle. The Man in the Moon will seem less mysterious now than he did when this bargain reprint was first written in 1959.

The second book is up-to-date. It keeps the young experimenter focused on one small square in the backyard—"your own or someone else's"—and shows how to uncover there clues to how all living things are connected. You need to dig, to collect and trap, to note down and draw, to try out foods, and you will learn how those animals and plants "make a living." The book has many diagrams and images to help identify the tiny animals—most of them do not have bones—you are most apt to find in your square, down to the rocky subsoil. Even those who stay indoors just to read this inviting book on wintry evenings will surely gain.

***From* One Small Square**



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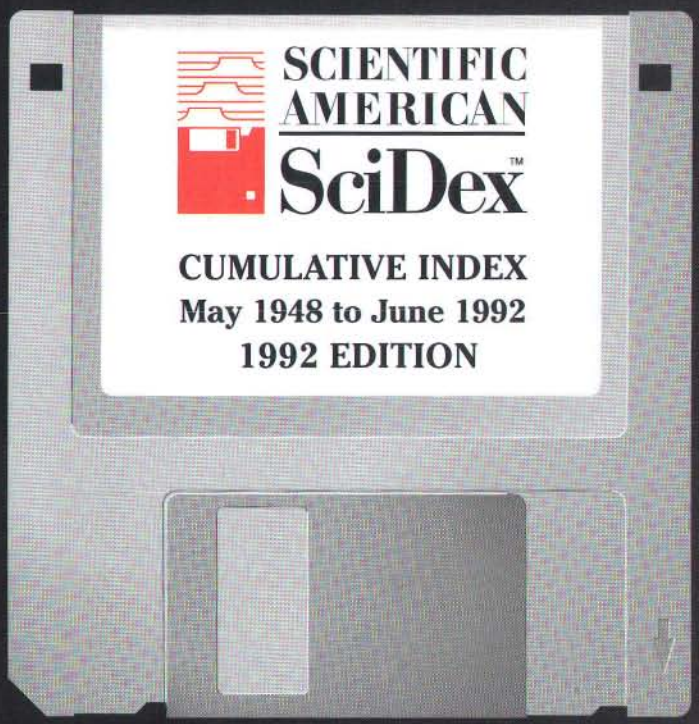

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ESSAY by Anne Eisenberg

Eponymous Science

Buckminsterfullerene (C_{60}) is a carbon allotrope with the symmetry of a soccer ball. Buckminsterfullerene is also an eponym, a word or phrase, like Turing test, Bunsen burner, galvanize or dahlia, that is derived from the name of a person or place. In the case of the carbon allotrope, the source is R. Buckminster Fuller, deviser of the geodesic domes so vividly called to mind by C_{60}'s molecular structure. C_{60} molecules are affectionately known as buckyballs.

Many scientists—the late Richard Feynman, for example—dislike eponyms, preferring instead informative, descriptive phrases. (Of course, today we have Feynman diagrams, the Feynman-Hellmann theorem and the Feynman-Vernon-Hellwarth representation.) Nomenclature committees, too, are enemies of the eponym. Charged with bringing logic to the terminology of their fields, they often attack eponymous terms as glorified forms of name-dropping: awkward, whimsical, inaccurate, archaic—and entirely too personal. But despite the best efforts of generations of linguistic reformers, eponyms continue to pour into the lexicon, glimmers of sentiment, ego and even wit in the flat, dispassionate prose of science.

The etiquette of eponym bestowal varies from field to field. In astronomy, comets are immediately and automatically named for the person who first observed them. In many other areas, though, scientists must first do the work and then hope friends will do the honoring. As M. P. Crosland said in his study of early scientific terminology, "It was not usual for a man to donate his own name to a substance. He relied on his contemporaries for this."

Now as then, discoverers who wish to crown themselves need some artifice. Lillian M. and Frank B. Gilbreth, who established an engineering consulting firm specializing in time-motion studies (Frank Gilbreth went on to tell the story of the family household in *Cheaper by the Dozen*), needed a new unit of measure to describe work activities such as repeated grasping or searching. The Gilbreths decided to coin this unit in honor of themselves. True, many units of measure are eponymous—the joule, watt, ohm, ampere, coulomb, farad, franklin and curie, among many others—but as a rule the units are named *for* the scientists, not *by* them. The Gilbreths named the unit of measure, still in use today, the "therblig"—Gilbreth in disguise—and thus modestly concealed its origin.

Samuel C. C. Ting, too, decided to hide his name in one of his findings, the *J* particle. The detection of this particle was announced the same day by both Ting at Brookhaven National Laboratory and Burton Richter at the Stanford Linear Accelerator Center. At Stanford, it was named the psi particle because of the resemblance of the paths made by daughter particles to the Greek letter psi. At Brookhaven, Ting dubbed the particle "J," in part because the letter J resembled the Chinese character for Ting. "Ting [is] a man who is not known for his modesty," one writer sniffed.

Mineralogists, according to the *Encyclopedia of Mineralogy*, have "almost complete freedom" in selecting names. Most often the people who describe new minerals choose names honoring a distinguished person. Once surnames are used up, discoverers have settled on two further choices: the given name (cliffordite for Clifford Frondel after frondelite was taken) or the full name (tombarthite, since barthite was already in the literature for Tom F. Barth). Mineralogists also favor places as name-givers, as do chemists: Ytterby, Sweden, yielded four elements—yttrium, terbium, erbium and ytterbium.

Eponymous locations also show up in medical terminology (Rocky Mountain spotted fever), as does the occasional patient's name. Bacitracin, an antibiotic salve, was obtained from a bacillus first isolated in the body of a child named Margaret Tracy (baci + Tracy + in). At one time, the distinction between the name of a patient or location and the name of the discoverer was neatly signaled by the absence or presence of '*s:* no '*s* with location (Lyme disease) or patient (Duffy blood factor); '*s* with a discoverer (Bright's disease, and thus S. J. Perelman's comment, "I have Bright's disease and he has mine"). This distinction, though, is vanishing—the possessive is increasingly dropped from eponyms, as can be seen in the recent entries in medical dictionaries.

The Swedish botanist Linnaeus instituted the first system of binomial nomenclature; in the midst of his linguistic reforms, he paused to consider eponyms and decided to leave them alone—he felt it was his "religious duty" to preserve in generic terms the names of great botanists. Linnaeus knew of the pleasure such designations bring, for when he named a wild mint *collinsonia* after naturalist Peter Collinson, Collinson exclaimed that he had been given "a species of eternity."

Opponents of scientific eponomy are not so rapturous. They take issue not only with the emotional associations eponyms evoke but with their ambiguity—for example, when a name like Charcot or Paget is used for two different diseases. They also object to the hyphens so useful in joining eponymous trios like Einstein, Podolsky and Rosen. Granted, the hyphen can be troublesome in this construction. The beginner considering the Lennard-Jones potential may reasonably think that two people did the work, only to find that Lennard-Jones is a single, British entity. Or the novice could expect the Hanbury-Brown-Twiss interferometer to concern a threesome (actually they are a duo—Hanbury-Brown and Twiss). The hyphen is handy in eponyms, though, capable of indicating both collaborative work and sequence of the findings. The Wentzel-Kramers-Brillouin approximation was originally named in honor of the three physicists who developed the technique; then it was brought to light that Jeffreys, a mathematician, had done the approximation well before the three physicists. "Jeffreys" was neatly added to the front of the eponym.

True, the billing in the Jeffreys-Wentzel-Kramers-Brillouin approximation gets a bit crowded, but that's a trifle for the scientific community, which is in no hurry to curb these quirky, egocentric tributes to its heroes. One observer even credits a "cult of personality" for the eponym's endurance. Perhaps scientists like the eponymic brevity with which several words—for instance, "Planck's constant"—can evoke so many others—for instance, "the constant of proportionality relating the energy of a quantum of electromagnetic radiation to its frequency." That's just the kind of economy highly prized by any believer in, say, Occam's razor.

ANNE EISENBERG, the author of four books on scientific writing, teaches at Polytechnic University in Brooklyn.

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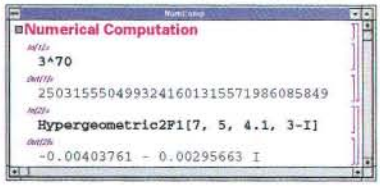

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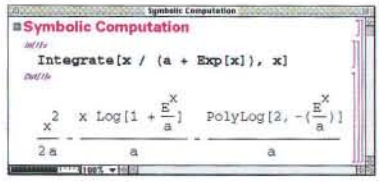

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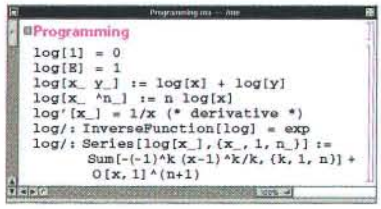

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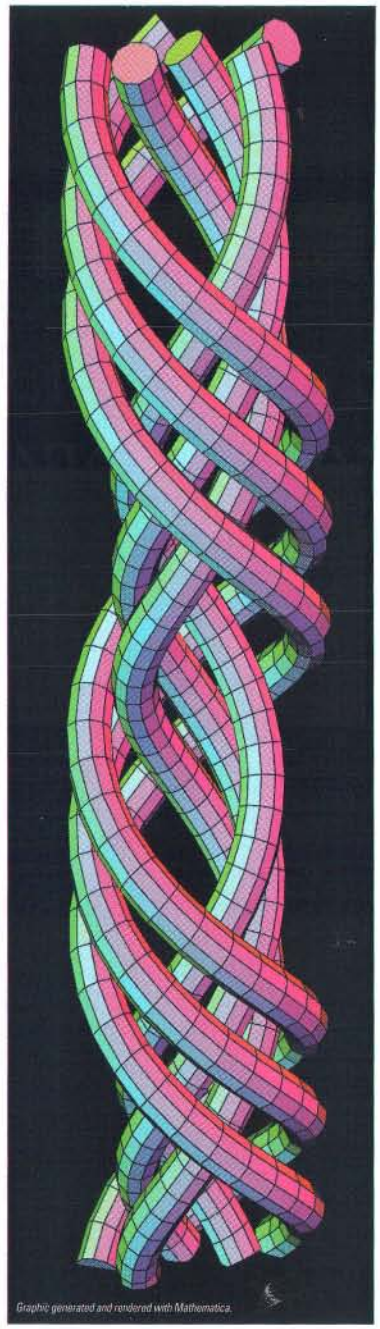
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